

5 Vascular and other dementias

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The non-Alzheimer dementias are a heterogeneous group of disorders, accounting for approximately a third of all dementias. Many dementias have familial forms and molecular techniques have identified the gene mutations responsible for Alzheimer's disease, Huntington's disease, familial Creutzfeldt–Jakob disease and a form of vascular dementia. These genetic defects lie at the start of pathological cascades which lead to disease, and they provide a powerful means of classification. This will hopefully extend to the other dementias with familial forms, such as vascular, and frontal lobe dementias.

Vascular dementia

Presentation

Vascular disease is the second most common cause of dementia after Alzheimer's disease. In addition to those individuals with a 'pure' vascular dementia, many individuals have clinical and pathological evidence of both Alzheimer's disease and vascular disease. The presentation of vascular dementia is variable and the clinical spectrum is wide. Patients may present with an insidious onset of cognitive problems, suggestive of a degenerative dementia, or with a series of strokes and widespread physical abnormalities.

Vascular dementia can be divided on clinical features into three major subtypes, although individuals may have features of more than one subtype: cognitive deficits following a single stroke, multi-infarct dementia and progressive small vessel disease (Binswanger's disease). There are also rare causes of vascular dementia (Box 5.3).

Cognitive deficits following a single stroke

The major causes of stroke (haemorrhage, infarct and embolism) can all produce dementia, although many single strokes leave little apparent cognitive deficit. When there are cognitive problems following a stroke, the site of the lesion usually determines the clinical

Box 5.1 Key features of the ICD-10 classification of vascular dementia (World Health Organization, 1992)

Vascular dementia

A dementia resulting from vascular disease
 Uneven impairment of cognitive function
 Abrupt onset or stepwise deterioration
 Focal neurological signs and symptoms
 May coexist with Alzheimer's dementia

Multi-infarct dementia

More gradual onset
 Follows a number of minor ischaemic episodes

Subcortical vascular dementia

A history of hypertension
 Deep white matter ischaemia
 Cerebral cortex is well preserved

picture. For example, a dominant middle cerebral artery infarct results in dysphasia, dyscalculia and dysgraphia. The dementia tends to be particularly severe in certain midbrain or thalamic strokes. Few patients have formal neuropsychological assessment following a single stroke and it is likely that many mild cognitive deficits are not detected. As with physical disability, the cognitive problems may remain fixed or recover, partially or totally.

Multi-infarct dementia

In a classical case of multi-infarct dementia there is a history of successive strokes, each leading to greater cognitive deficits. These strokes produce a step-like deterioration, with intervening periods when patients remain stable (or may improve). Multi-infarct dementia can be produced through similar mechanisms to a single stroke. The recurrent nature of multi-infarct dementia suggests that there is underlying disease predisposing to stroke, such as hypertension or valvular heart disease. Multi-infarct dementia can be produced by large vessel disease, small vessel disease or a combination of the two.

Progressive small vessel disease (Binswanger's disease)

In Binswanger's disease the diagnosis may initially be less clear. The course is of a slow intellectual decline, either gradual or step-like.

The clinical picture may be dominated by the dementia, or there may be concomitant physical problems, such as gait disorders or dysarthria. Brain imaging reveals periventricular lucencies and extensive white matter changes. The changes are often particularly marked on magnetic resonance imaging. There may be small distinct infarcts (lacunae), or more generalised white matter changes (leukoariosis). This distribution of the radiological and pathological changes suggests that the disease is affecting the small perforating vessels. This subtype of vascular dementia has had a number of names, including Binswanger's disease and subcortical arteriosclerotic encephalopathy. The cognitive profile of progressive small vessel disease is suggestive of a subcortical dementia, with slowing of intellectual processes, rather than the specific deficits such as dysphasia and dyscalculia, produced by large cortical strokes.

Epidemiology

Vascular disease contributes to about a quarter of all cases of dementia in published series. Vascular dementia shows marked geographical and racial variation and, not surprisingly, is common in countries such as Japan which have a high incidence of vascular disease. The prevalence of vascular dementia is higher with increasing age and in males. Patients often have a family history of vascular disease. There are many medical associations of vascular dementia, including hypertension, diabetes, hyperlipidaemia, polycythaemia, homocystinuria, sickle cell anaemia, coagulopathies and valvular heart disease. Vascular disease is more common in smokers. In a few families there is an autosomal dominant pattern of inheritance, with onset around the age of 45. This syndrome has been termed cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Clinical features

The variety of presentations of stroke are legion, and so are the features of vascular dementia. The differential diagnosis is usually between vascular dementia and a degenerative dementia, although treatable causes of dementia must not be forgotten. There are certain clinical features, such as the sudden onset of a deficit, which are highly suggestive of vascular dementia. A scoring system was developed by Hachinski and colleagues (1975) which allows the clinician to quantify the likelihood of a patient having a vascular, rather than degenerative dementia (Box 5.2). A score above six suggests vascular dementia.

On examination there may be clues to the aetiology of the dementia: physical signs such as a hemiparesis, hemianopia or

Box 5.2 The Hachinski ischaemia score (adapted from Hachinski *et al*, 1975)

Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History of hypertension	1
History of strokes	2
Atherosclerosis	2
Focal neurological symptoms	2
Focal neurological signs	2

pseudobulbar palsy are typical features of a vascular dementia and unusual in degenerative dementias. As well as performing a neurological examination, it is important to record the blood pressure and look for evidence suggestive of extracranial vascular disease. The presence of significant cardiac murmurs or atrial fibrillation should prompt further investigations. The presence of carotid bruits or absent foot pulses signifies clinical vascular disease.

Investigations

Investigations need to be tailored to the individual patient. Blood tests include a full blood count, erythrocyte sedimentation rate, biochemical screen, syphilis serology, lipids, B12 levels and thyroid function tests. An electrocardiogram and chest X-ray should be done. In young-onset patients and patients in whom embolic disease seems likely (patients with large discrete infarcts affecting several vascular territories), an echocardiogram is appropriate to look for a cardiac source of emboli. Trans-sternal echocardiography is often used as a screening test for cardiac defects, but transoesophageal echocardiography is a more sensitive investigation. If there is history of an event in a carotid territory and the patient is suitable for surgery, a Doppler ultrasound of the carotid vessels should be performed to look for a surgically treatable stenosis. Brain imaging is often appropriate to exclude treatable forms of dementia and to confirm the presence of macroscopic infarcts or periventricular lucencies.

In unusual cases many more investigations may be done, including a prothrombotic screen, autoantibody screen and tests aimed at looking for rare neurological diseases such as mitochondrial disease,

Fabry's disease and homocystinuria. There are several causes of strokes which typically occur in young people without obvious vascular risk factors. These include the lupus anticoagulant syndrome, arterial dissections and paradoxical embolism from a deep venous thrombosis through a patent foramen ovale. These diagnoses are important because medical treatment may reduce the risk of future strokes, however they are extremely rare causes of vascular dementia.

Management

The most important initial step in the management of vascular dementia is to search for the treatable causes of stroke. If there is a cardiac source of emboli, such as an enlarged, fibrillating atrium or valvular heart disease, many patients will benefit from anticoagulation. If there is a history of a vascular event within a carotid territory and a significant stenosis of that artery, carotid endarterectomy or angioplasty may be indicated. Medical diseases such as hypertension, hyperlipidaemia and diabetes should be treated by diet or drugs. Aspirin may be prescribed in cases of vascular dementia, in whom there is no contraindication, although there are no trials to suggest it slows the progression of the disease. It is important also to manage problems produced by the dementia, such as disinhibited behaviour and depression (see Chapter 6).

Preventive measures in the population offer the best means of reducing the incidence of vascular dementia. Initiatives such as the UK Government's *Health of the Nation* targets (Department of Health, 1992) seek to do this by promoting dietary changes and regular exercise. Treatment of hypertension is important as relatively small decreases in mean diastolic blood pressure can substantially reduce the risk of stroke.

Prognosis

The prognosis of vascular dementia is poor, and may be worse than Alzheimer's disease. Most patients die within a few years of the onset of the dementia. Clearly, if there is a treatable cause such as a valvular heart lesion, then the disease progression can be halted, however often the cognitive decline continues despite treatment of risk factors. The poor prognosis emphasises the importance of preventative measures.

Rare causes of vascular dementia

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

CADASIL is a familial form of vascular dementia (Tournier-Lasserre *et al*, 1993). The term CADASIL for this disease was adopted by the French

group and is now widely accepted; although there are several reports of a similar disease in the earlier literature. Patients with CADASIL usually present with recurrent stroke, at an average age of 43 years. There is often a history of migraine, and many patients later develop a subcortical dementia and pseudobulbar palsy. Magnetic resonance imaging shows widespread white matter changes and is often abnormal in presymptomatic relatives at risk of developing the disease. The disease is transmitted as an autosomal dominant trait with high penetrance. Several pedigrees have been described, mainly from continental Europe. Molecular genetic linkage studies have assigned the disease gene to the long arm of chromosome 19. Recent work has associated mutations in the Notch 3 gene on chromosome 19 with CADASIL in several families.

Vasculitis

Patients with a cerebral vasculitis may develop cognitive problems and dementia, as a result of repeated infarcts. The history of dementia may be steadily progressive or step-like, but is usually of rapid progression compared with the degenerative dementias. There are often marked systemic features with the vasculitis involving several different organs, but the clinical features may be limited to the central nervous system. The more common causes of cerebral vasculitis include systemic lupus erythematosus, giant cell arteritis, isolated cerebral vasculitis and polyarteritis nodosa. The diagnosis can sometimes be made through a series of autoantibody tests including: double stranded DNA and ANCA (antineutrophil cytoplasmic antibody); looking at inflammatory markers; brain imaging; examination of the cerebrospinal fluid; and the search for evidence of vasculitis in other affected organs. In many cases the diagnosis is less clear, and cerebral angiography and cerebral or meningeal biopsy may be needed.

Cerebral haemorrhage

In acute cerebral haemorrhage and extracerebral haemorrhage, dementia is not usually the presenting problem but patients are often left with residual cognitive problems. Large arteriovenous malformations can cause cognitive problems through pressure and steal effects, or through cerebral haemorrhage. There are also two autosomal dominant forms of vascular dementia associated with repeated lobar haemorrhages:

- (a) Hereditary cerebral haemorrhage with amyloidosis, Dutch type. This condition is caused by mutations in the amyloid precursor protein gene and is associated with the deposition of beta amyloid.

- (b) Hereditary cerebral haemorrhage with amyloidosis, Icelandic type. This is caused by mutations in the cystatin C gene and is associated with cystatin C deposition.

Chronic subdural haematoma

Chronic subdural haematoma is one of the more common treatable causes of dementia. The patient is usually elderly and there may be no history of previous trauma. If the haematoma is unilateral, the patient presents with features of a lateralised space occupying lesion. If the subdurals are bilateral, then the diagnosis may be more difficult. Examination often reveals clues to the diagnosis, such as papilloedema or bilateral extensor plantar responses.

Other vascular dementias

Dementia can also be produced by multiple infarcts occurring during hypotensive crises. Such infarcts typically affect the watershed areas of the brain, which lie between two vascular territories. These infarcts may occur in the survivors of cardiac arrest. Cognitive problems can also follow myocardial infarction and cardiac surgery.

Non-Alzheimer degenerative dementias

Dementia with Lewy bodies

Patients who present with Parkinson's disease may develop a progressive dementia. A subgroup of Alzheimer's disease type patients develop marked extrapyramidal problems. Pathological examination of patients dying with these two clinical pictures often reveals the presence of cortical Lewy bodies (Kosaka *et al*, 1988). These are seen particularly well with anti-ubiquitin staining. Such patients are described as having dementia with Lewy bodies (formally called cortical Lewy body disease, and diffuse Lewy body disease, among other names). Dementia with Lewy

Box 5.3 Types of vascular dementia

Cognitive deficits following a single stroke
Multi-infarct dementia
Progressive small vessel disease (Binswanger's disease)
CADASIL
Vasculitis
Cerebral haemorrhage
Chronic subdural haematoma

bodies is one of the more common degenerative dementias. However, there is clinical and pathological overlap in these patients with Alzheimer's disease and idiopathic Parkinson's disease. Clinical features strongly suggestive of dementia with Lewy bodies include rapid fluctuations in cognitive ability and visual hallucinations (Box 5.4). Treatment with l-dopa and the standard anti-parkinsonian drugs often improves the motor symptoms, but can lead to confusion and hallucinations. Patients are very sensitive to neuroleptics, which can considerably worsen the Parkinsonian symptoms.

Frontotemporal dementia

A significant minority of patients with a degenerative dementia present with symptoms such as personality change and behavioural problems, suggestive of frontal lobe dysfunction. In some series, up to 20% of cases of degenerative presenile dementia present with this anterior cortical picture rather than the typical temporoparietal deficits seen in Alzheimer's disease (Gustafson *et al*, 1992). The disease progresses and patients tend to develop a non-fluent aphasia. Patients often develop features suggestive of temporal lobe dysfunction, such as hyperorality. In contrast to Alzheimer's disease, memory is affected later and less severely. Spatial orientation is well-preserved, even late in the illness. Insight is characteristically lost early.

On post-mortem examination the pathological features are variable. In the majority of cases there is mild frontal and temporal lobe atrophy, without the distinctive histopathological features such as plaques, tangles and intraneuronal inclusion bodies seen in other degenerative dementias. This syndrome has been described under many names, including frontal lobe degeneration of non-Alzheimer type. Following a consensus statement it is now called frontotemporal dementia (Brun *et al*, 1994).

There is a high proportion of familial cases, about 50% of presenile cases having a positive family history for dementia. Recently, one of the mutations responsible for this form of dementia has been mapped to chromosome 3 (Brown *et al*, 1995). The dementia in other families is linked to a locus on chromosome 17 (Wilhelmsen *et al*, 1994). The disease is steadily progressive and there is no specific treatment. Patients with clinical frontotemporal dementia may have a variety of other pathological features, including those of motor neuron disease in the absence of the typical clinical signs of these diseases (Cooper *et al*, 1995).

Pick's disease

Pick's disease is currently regarded by most authorities as a form of frontotemporal dementia. It is differentiated from the other forms of

Box 5.4 Features of frontotemporal dementia

Personality change
Early loss of insight
Non-fluent aphasia
Hyperorality
Well-preserved spatial orientation

frontotemporal dementia by pathological features, such as severe 'knife-edge' atrophy of the frontal and temporal lobes and the presence of argyrophilic inclusion bodies (Pick bodies) in neurones. Swollen, achromatic neurones (also called ballooned neurones or Pick cells) are present in other neurodegenerative diseases and do not reliably identify Pick's disease. The clinical features do not distinguish it from other forms of frontotemporal dementia; it may present with the features of a frontal lobe dementia, or less frequently, with features of selective temporal lobe disease. Classical Pick's disease is the cause of a small minority of cases of frontotemporal dementia. There are rare published reports of familial classical Pick's disease (many of the reported familial cases have clinical frontotemporal dementia without the pathological features of Pick's disease) (Brown, 1992).

Dementia associated with other neurological diseases

Many neurological diseases, including motor neuron disease, progressive supranuclear palsy and multiple sclerosis, are associated with dementia. Often the dementia occurs in patients who have had these diseases for many years, but occasionally dementia can be an early or presenting feature. The cognitive assessment of these patients is often complicated by their physical problems.

Huntington's disease

There are many genetic causes of dementia, the best known of which is probably Huntington's disease. This condition may present with cognitive problems, or a movement disorder. It is inherited as an autosomal dominant trait. The mutation producing the disease has been identified (Huntington's Disease Collaborative Research Group, 1993). The disease arises as a result of an abnormal expansion of a trinucleotide repeat sequence within the gene. This is one of a group of so called 'triplet repeat disorders', which can produce neurological disease. The gene product has been named Huntingtin. The disease can now be diagnosed using molecular genetic techniques.

Prion dementia

These are a clearly defined group of disorders characterised by an accumulation of an abnormal form of a normal human protein, prion protein (Prusiner, 1991). The first human form, Kuru, was described in the cannibal Fore people in New Guinea. Gadjusek and colleagues showed that Kuru was transmissible to chimpanzees by intracerebral inoculation of a brain extract (Lampert *et al*, 1969). Neuropathological morphological similarities were noted between Kuru and Creutzfeldt–Jakob disease, a rare disease first described in Europe. Gadjusek and colleagues showed that Creutzfeldt–Jakob disease was also transmissible.

Creutzfeldt–Jakob disease is a rare disease, affecting about one person per million per year. Affected individuals develop a rapidly progressive dementia with cerebellar ataxia and myoclonus. Typical cases die within a few months of onset of the disease. Neuropathological examination reveals spongiform degeneration. Immunocytochemistry shows the deposition of prion protein. Familial forms of prion disease account for about 15% of all cases. Some patients have clinical features very similar to sporadic cases. Two variants have been described:

- (a) Gerstmann–Straussler syndrome, which has a more chronic course and prominent cerebellar ataxia.
- (b) Fatal familial insomnia, which presents with insomnia and a thalamic dementia.

A series of mutations in the prion protein gene on chromosome 20 have been shown to cause the familial forms. Iatrogenic cases of Creutzfeldt–Jakob disease have been reported following neurosurgery and injection of growth hormone obtained from pooled human cadavers. Recent evidence suggests that a new form of Creutzfeldt–Jakob disease may have appeared in the UK, as a result of people eating offal from cows suffering from a bovine prion disease (bovine spongiform encephalopathy, BSE).

Box 5.5 ICD–10 other diseases causing dementia (World Health Organization, 1992)

Pick's disease
Creutzfeldt–Jakob disease
Huntington's disease
Parkinson's disease
Human immunodeficiency virus disease

Treatable dementias

Metabolic and endocrine

Dementia is such a devastating disease that it is important to consider a treatable cause in all patients (Box 5.6). Virtually any metabolic or endocrine derangement can cause cognitive problems, and simple blood tests should be performed to exclude metabolic causes for cognitive problems, including renal disease, liver disease and hypothyroidism.

Infective

Neurosyphilis is now a very rare cause of dementia, but should be considered in all cases of dementia since it is treatable. Patients with positive serology require further investigation, usually including a cerebrospinal fluid examination and a full course of antibiotic treatment. Problems in diagnosis may arise with patients who have been exposed to other treponemal diseases, such as yaws.

The acquired immune deficiency syndrome (AIDS) can produce dementia through direct invasion of the brain by the virus, or as a result of a number of associated central nervous system infections and neoplasms. In neurological practice it is a very rare cause of dementia in patients not previously known to have human immunodeficiency virus (HIV) infection.

Whipple's disease is almost certainly an infective disease which produces a dementia. There are often clues to the diagnosis, with a history of intestinal problems and systemic symptoms. The physical examination may reveal typical signs, such as a supranuclear gaze palsy. Magnetic resonance image scanning typically shows both grey and white matter lesions. Treatment is with long-term antibiotics.

Vitamin deficiencies

Several vitamin deficiencies can cause cognitive decline. It is important to screen for B12 deficiency in all patients with dementia,

Box 5.6 Treatable dementias

Metabolic and endocrine: renal disease, liver disease, hypothyroidism

Infections: neurosyphilis, HIV, Whipple's disease

Vitamin deficiencies: B12, folate, nicotinic acid, thiamine

Toxins and drugs: anticonvulsants, alcohol

Neoplastic

Normal pressure hydrocephalous

and to be aware that not all have the characteristic haematological abnormalities. Folate deficiency and nicotinic acid deficiency, among other vitamin deficiencies, may also produce cognitive problems.

Thiamine deficiency can produce an acute encephalopathy, Wernicke's encephalopathy, which is preventable. Furthermore, it can be an iatrogenic disease precipitated by infusion of glucose into patients at risk of thiamine deficiency. The most common cause of thiamine deficiency is alcohol misuse, but it can occur in patients with malabsorption syndromes or malignancy. Wernicke's encephalopathy is characterised by: ophthalmoplegia (typically bilateral lateral rectus palsies), nystagmus, ataxia and disturbed consciousness.

Wernicke's encephalopathy needs immediate treatment with intravenous thiamine. Chronically the condition is termed Korsakoff's psychosis and is characterised by loss of short-term memory. Patients often confabulate; psychometry usually reveals widespread deficits, including problems in remote memory.

Toxins and drugs

Toxins and drugs should be excluded as causes. Alcohol has been suggested as a cause of dementia, but people with chronic alcohol dependency often have other associated conditions such as vitamin deficiencies, head injuries and subdural haematomas. Many drugs have been found to cause cognitive problems, common examples include the anticonvulsants. Most drug-induced cognitive changes are reversible on withdrawal of the drug, although the recovery may be slow.

Neoplastic

Neoplasms can produce dementia in three main ways:

- (a) Through local effects of the primary growth. There may be few associated neurological symptoms and signs, particularly with frontal tumours. Many such tumours are intrinsic gliomas and the long-term prognosis is poor, but dementia can be produced by meningiomas, which are curable.
- (b) Through secondary spread.
- (c) Through para-neoplastic mechanisms such as brainstem encephalitis or progressive multifocal leukoencephalopathy.

Normal pressure hydrocephalus

Normal pressure hydrocephalus produces a clinical triad of: progressive dementia, urinary incontinence and gait disturbance

The dementia is of the subcortical type, with marked cognitive slowing, in the absence of focal cortical deficits. There may be a

history of subarachnoid haemorrhage or meningitis. It can be very difficult to distinguish normal pressure hydrocephalus (where the hydrocephalus causes the symptoms) from patients with degenerative or vascular dementia with periventricular atrophy (where the hydrocephalus is secondary to cerebral atrophy). In the past, normal pressure hydrocephalus was overdiagnosed, it is probably a very rare cause of dementia. It is possible to make a definite diagnosis with intraventricular pressure monitoring, but this is invasive and not always conclusive. Some patients show a temporary improvement following lumbar puncture to remove 20–50 ml of cerebrospinal fluid, to lower the cerebrospinal fluid pressure. Treatment is difficult. A few patients improve dramatically following insertion of a permanent shunt. However, others are left worse off as a result of the complications of shunting, such as shunt infections and subdurals.

Conclusion

There are many causes of dementia, some of which are treatable. Advances are being made into the genetic basis of these disorders and this should help diagnosis, prevention and treatment. Good practice demands the thorough assessment of all patients presenting with dementia.

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