Chapter 22
Multiple comorbidities

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Key points

- Differentiating whether a dementia syndrome is due to Alzheimer's disease, cerebrovascular disease or mixed origin may be challenging as they present similar risk factors and cognitive profiles.
- More than 80% of the global burden for stroke is attributable to modifiable risk factors.
- Better understanding of the determinants of vascular contributions to cognitive disorders is required.
- Risk of malnutrition and subsequent vitamin deficiencies are strongly correlated with cognitive decline and nutritional status should be routinely explored.
- In the case of ventriculomegaly, it is important to evaluate the presence and severity of the key symptoms and signs of idiopathic normal pressure hydrocephalus (gait changes, cognitive decline and urine incontinence).

This is a chapter of the *World Alzheimer Report 2021, Journey to a Diagnosis of Dementia* which can be accessed in full at: https://www.alzint.org/resource/world-alzheimer-report-2021/

General background

Most people over the age of 75 have an assortment of medical conditions that may explain, to a certain extent, memory and other cognitive complaints and how they impact activities of daily life. The clinician performing the diagnostic assessment must prioritise these different medical conditions after evaluating the information provided by the individual's medical history, physical examination, and laboratory tests including brain imaging.

The following essays highlight some of the most common conditions influencing the deliberation of a dementia diagnosis, its causes and management. This may include differentiating between dementia caused by Alzheimer's disease and a dementia of vascular origin. Topics range from stroke to nutritional deficits, as well as the surprisingly common anomaly called ventriculomegaly, or enlarged cerebral ventricles, diagnosed upon analysis of brain scans.

Expert essay

The differential diagnosis between Alzheimer's disease and vascular dementia, including the concept of mixed dementia

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Challenges inherent to the differentiation

Differentiating whether a dementia syndrome is due to Alzheimer's disease, cerebrovascular disease or a contribution from both (mixed Alzheimer's disease and CVD) can be challenging given that some of the associated risk factors such as age, hypertension and diabetes as well as their cognitive profiles tend to overlap. Yet, determining the contribution of Alzheimer's disease and/or cerebrovascular disease in accounting for the dementia syndrome is important as it will affect its prognosis or treatment of the syndrome. Further, as age is one of the strongest risk factors for both diseases, both co-occurring together is especially common among older people. Autopsy studies show that cerebrovascular disease pathology (for example, lacune, microinfarct, white matter changes, enlarged perivascular space, micro- or macro-haemorrhage, large infarct, atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy) co-occurs with Alzheimer's disease pathology (namely, amyloid beta [Aβ] and phosphorylated tau [p-tau]) in about 40–80% of dementia cases of older people. What's more, it has additive effects with Alzheimer's disease pathology in lowering cognitive function and increases the odds of dementia especially among those with less burden of Alzheimer's disease pathology (1,2). Given this close association between Alzheimer's disease and CVD, the aetiological contribution to a dementia syndrome for an individual may fall somewhere along a spectrum, with pure Alzheimer's disease at one end of the spectrum and pure cerebrovascular disease at the other end (Figure 1). Other brain pathologies (for example, Lewy bodies) can also mix with Alzheimer's disease and/or cerebrovascular disease.

Mixed dementia involving non-Alzheimer's disease/cerebrovascular disease pathology is not as common as mixed Alzheimer's disease and CVD and will not be discussed further in this essay.

In the context of progressive cognitive decline

Although Alzheimer's disease is characterised by a slowly progressive cognitive decline associated with predominant memory impairment at the initial stage, age-related sporadic cerebral small vessel disease may also present with similar clinical manifestation and may be misdiagnosed as Alzheimer's disease (3). Cerebral small vessel disease is the most common type of cerebrovascular disease associated with cognitive impairment and dementia. A typical cognitive profile of small vessel disease includes prominent executive dysfunction, slow processing speed and memory impairment. Note that the memory impairment in small vessel disease is due to problems retrieving previously encoded information and can be improved with cueing or recognition. This differs from Alzheimer's disease where the problem lies with encoding and storage of information. A neuropsychological assessment battery that evaluates executive function, processing speed and recognition memory may help to clinically differentiate small vessel disease from Alzheimer's disease (4). Other patterns of temporal evolution include acute decline or stepwise deterioration related to stroke event(s) (5). Clinical features that may suggest SVD include parkinsonism, particularly affecting the lower body, upper motor neuron signs (for example, hemiparesis with brisk reflex and extensor plantar response) or pseudobulbar palsy (6). These features may or may not occur in association with the symptoms of a stroke (6). Cerebral small vessel disease can exist on its own while also commonly found to co-occur with Alzheimer's disease. Clinical studies show that among individuals diagnosed with Alzheimer's disease, prevalence of early confluent to confluent white matter hyperintensity (WMH) (refer to Chapter 13) was found to increase from 20% in those under 60 years of age to almost 50% in those over 80 years of age (7). Concurrent presence of small vessel disease in Alzheimer's disease is associated with a more rapid conversion from mild cognitive impairment to dementia (6). Given that direct visualisation of the brain small vessel

with conventional imaging techniques is difficult, in vivo assessment of small vessel disease depends on detecting the impacts of small vessel disease upon the brain parenchyma, which is best seen on MRI. Conventional MRI biomarkers of small vessel disease include WMH, lacunes, microbleeds and enlarged perivascular space (6).

Overall, since SVD may mimic the clinical presentation of Alzheimer's disease, those presenting with progressive cognitive decline characterised by memory complaints may be misdiagnosed as having Alzheimer's disease if a structural brain imaging such as an MRI is not performed. Noteworthy is that if the MRI reveals features of SVD (for example, confluent WMH and/or multiple lacunes), the progressive cognitive syndrome may be due to either pure SVD or to mixed Alzheimer's disease and SVD. In this scenario, medial temporal lobe atrophy (MTA), which is considered an imaging biomarker of Alzheimer's disease, (Chapter 13) may not be a helpful pointer of Alzheimer's disease because it is also associated with small vessel disease. Additional investigations that could detect specific Alzheimer's disease pathology (that is, Aβ and p-tau) may become important. At present, these investigations may include amyloid and tau positron emission tomography (PET) or cerebrospinal fluid (CSF) analysis for Aβ42 (or the Aβ42/Aβ40 ratio) and p-tau (for example, p-tau 181, p-tau 217), which are accessible in more specialised centres. Recent development of blood-based platforms will likely enable easier detection of molecular biomarkers of Alzheimer's disease in daily clinical practice (8).

In the context of stroke

For people presenting with acute cognitive decline immediately after a stroke, it is likely that a vascular component is responsible for the cognitive decline. However, this does not mean that concurrent Alzheimer's disease pathology can be excluded. In fact, concurrent Alzheimer's disease pathology is not unusual in the context of a stroke and its presence increases the odds of developing dementia after a cerebrovascular event (5). A study using in vivo amyloid PET shows that about 30% of people with new onset dementia after a stroke or transient ischemic attack (TIA) have concurrent Alzheimer's disease pathology and this prevalence is about four times higher than that found in those who do not develop dementia after stroke/TIA (9). For those individuals who develop dementia after an acute cerebrovascular accident, they are more likely to have concurrent Alzheimer's disease pathology contributing to the dementia syndrome if the acute lesion is not prone to induce cognitive impairment (for example, TIA with no evidence of ischaemic brain tissue on imaging or if the lesion is not located at a strategic location) and imaging do not reveal severe chronic cerebrovascular disease burden (for example, multiple old infarcts or confluent WMH) (5). A high index of scepticism for concurrent Alzheimer's disease is needed in such clinical scenarios. Strategic locations for inducing post-stroke cognitive impairment include left frontotemporal lobes, left thalamus and right parietal lobe (10). Moreover, for those with concurrent Alzheimer's disease, their rate of cognitive decline is much faster than those without it (5). However, a slowly progressive cognitive decline in stroke survivors does not necessarily imply the presence of concurrent Alzheimer's disease pathology. In fact, in the context of a stroke, the progressive decline in cognition is commonly associated with severe SVD, rather than with Alzheimer's disease (5). In general, to ascertain the presence or contribution of Alzheimer's disease in the context of a stroke, additional investigations (namely PET, CSF and/or blood tests) as previously stated will be required.

Conclusion

In summary, although certain clinical pointers may help to differentiate between Alzheimer's disease and CVD, clinical features overlap making the differentiation challenging. Accurate differentiation between Alzheimer's disease and CVD or mixed diseases will depend on investigations to detect respective biomarkers. An MRI is most helpful to estimate the presence and relevance of CVD. To date, use of PET or CSF analysis for the detection of Alzheimer's disease biomarkers is mostly restricted to specialised centres. Recent development in blood-based technologies will likely enable easier differentiation between Alzheimer's disease and cerebrovascular disease in clinical practice.

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Expert essay

Risk factors for cerebrovascular disease

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According to the top 10 causes of death in the world reported by the WHO, stroke ranks as number two, after ischemic heart disease in 2020. The number of deaths due to stroke increased from approximately 5.5 million in 2000 to 6.2 million in 2019, which is roughly 11% of the total deaths (1). Overall, the age-standardised total stroke prevalence rates are the highest in Oceania, South-east Asia, North Africa and the Middle East, and East Asia. Stroke or cerebrovascular disease is an acute disease that can occur within minutes to hours. The presenting symptoms vary from the common, such as weakness, hemisensory loss, and facial weakness to uncommon ones, such as apathy, abnormal movement, acute dementia, and more.

Strokes can be classified into two main categories: haemorrhagic and ischemic strokes. The majority of strokes, approximately 80%, involve ischemic stroke, which affects a variety of large and small vessels and is caused by multiple aetiologies, such as atherosclerosis, cardioembolic, lacunar or other specific causes. Of course, prevention is better than treatment. This Chapter will review the risk factors for cerebrovascular disease, focusing on the well-known risk factors (Figure 1).

Non-modifiable risk factors

1. **Age:** The prevalence of stroke increases with age, with the percentage of population affected doubling for each decade after the age of 40 (2). As countries around the world become ageing societies, the numbers of all stroke patients are rising in both men and women. Ageing alters both structure and function of micro- and macro-circulations. Age-related microcirculatory changes are presumably mediated by endothelial dysfunction, impaired cerebral autoregulation, and neurovascular coupling. Silent cerebrovascular diseases represent structural abnormalities that increase with advancing age and forecast increased risk of future symptomatic strokes (3).
2. **Gender:** The relationship between stroke and gender depends on age. Females have a higher lifetime risk of stroke than males. In the Framingham study, the lifetime risk of stroke among those 55 to 75 years of age was 1 in 5 for females and ~1 in 6 for males (2). Age-specific incidence rates are substantially lower in females than in males in the younger and middle-aged groups, but equal to higher in the oldest age groups.
3. **Ethnicity:** There are ethnicity disparities in stroke. Among the US population, the age-adjusted incidence of first ischemic stroke is higher in Black and Hispanic individuals compared to White individuals (3). In other parts of the world, for example in Southeast Asia, some countries in the region have higher age-standardised prevalence and mortality rates of total stroke (and ischemic stroke) than the US and most European countries (3).
4. **Genetics:** Those with a positive family or documented parental history of stroke before 65 years of age have an increased risk of stroke in offspring. Genetic influences on stroke risk can be considered on the basis of the influence on individual risk factors, the genetics of common stroke types, and uncommon or rare familial causes of stroke. Identification of the underlying gene for these disorders is important for diagnosis, counselling, and patient management (4).

Modifiable risk factors

1. **Hypertension** is a well-known and a strong risk factor for all strokes. Diagnosis of high blood pressure is intra-individual, based on measurement categories or differences in blood pressures at different time points. In accordance with most major guidelines, it is recommended that hypertension be diagnosed when a person's systolic blood pressure (SBP) is ≥140 mm Hg and/or their diastolic blood pressure (DBP) is ≥90 mm Hg (5). Since elevated blood pressure is related to all causes of death, cardiovascular events, heart disease, and stroke in both ischemic and haemorrhagic (6), early treatment and lifestyle change are recommended for all patients. The American Heart Association (AHA)/American Stroke Association (ASA) 2021 guideline for secondary stroke prevention suggested a target blood pressure of 130/80 mm Hg or lower for people with a high risk of stroke or previous stroke/TIA (7).

2. **Diabetic mellitus** can cause pathological changes in both small and large vessels leading to many serious complications, one of which is stroke. The diabetic duration correlated well with ischemic stroke risk, which increases 3% each year and triples for those with diabetes for ≥10 years (8). Furthermore, hyperglycaemia during the acute stroke phase is associated with poor outcomes and showed significantly poorer performance in global cognition and in all domains compared with individuals with normal fasting glucose level in 3–6 months after stroke (9).
3. **Dyslipidaemia:** The relationship between stroke and dyslipidaemia is tangible. High cholesterol and high low-density lipoproteins (LDL) increase the risk of ischemic stroke whereas high high-density lipoproteins (HDL) were known as a protective cardiovascular factor. Evidence for the direct influence of triglyceride to stroke is still being debated. Recent guidelines recommend more aggressive cholesterol lowering than in the past because it shows the benefit on coronary atherosclerosis plaque regression and significant reduction of cardiovascular death, myocardial infarction and ischemic stroke. However, very low cholesterol and LDL (<30mg/dl) has a potential side effect of intraparenchymal haemorrhage (10). For some ischemic stroke patients with previous haemorrhage, small vessel disease, or cerebral amyloid angiopathy, treatment at very low level of LDL should be made with caution.
4. **Smoking:** The risk of stroke correlates with the current smoking status, with higher numbers of cigarettes smoked per day showing a higher risk of stroke. Ischemic stroke seems to be more affected than haemorrhagic stroke (11). Smoking cessation rapidly reduces the risk of stroke, which nearly disappears 2–4 years after cessation (12).
5. **Physical inactivity** is one of the key risk factors in the INTERSTROKE study that accounted for more than 80% of the population attributable risk (PAR) for stroke (11). The relationship between physical activity and stroke reduction might be the effect of decreased blood pressure, blood level and body weight. Healthy adults should perform at least moderate to vigorous intensity aerobic physical activity at least 40 minutes/day for 3 to 4 days/week (4,12).
6. **Diet and nutrition:** It is likely that Mediterranean, DASH-style diets, or other diets that are low in sodium, contain plant-derived nutrients, have decreased caloric intake related to saturated and trans-fat, limit sweet intake and are rich in fruits and vegetables can reduce the stroke risk (4). For the nutrition supplement, folic or B vitamin (B6, B12) may be considered for prevention of ischemic stroke in patients with hyperhomocysteinemia, but its clinical outcome for reduced CVD risks or recurrent stroke was not well established (4).
7. Other risk factors
    a. **Obesity:** The waist-to-hip ratio (>0.91 in men and >0.86 in women) was attributed as a risk factor of stroke more than the overall increase in weight, as indicated by the body mass index. While there does not appear to be a direct correlation between weight loss and the risk of stroke, there may be an indirect effect as weight reduction helps to improve control of blood pressure, glucose level and myocardial infarction, which are the primary risk factors of stroke (11).
    b. **Metabolic syndrome** is a group of composite conditions that, based on the harmonious definition, includes high blood pressure ≥130/≥85 mm Hg or on medication, fasting glucose ≥100 mg/dL (>5.5 mmol/L) or on medication, abdominal obesity as determined by waist circumference >102 cm for men and >88 cm for women, abnormal HDL cholesterol <40 mg/dL (< 1.03 mmol/L) for men and <50 mg/dL (<1.30 mmol/L) for women and triglyceride levels ≥150 mg/dL (≥ 1.7 mmol/L). The combination of these risk factors correlated with increased stroke risk. Management of individual components of the metabolic syndrome is recommended, including lifestyle measures (such as exercise, appropriate weight loss and proper diet) and pharmacotherapy (for example, medications for BP lowering, lipid lowering, glycaemic control, and antiplatelet therapy).
    c. **Alcohol intake:** The effect of alcohol may depend on the level of consumption. Light-to-moderate alcohol consumption (≤2 drinks per day in men and ≤1 drink per day in women) may have a protective effect against stroke, due to the higher levels of HDL cholesterol, reduced platelet aggregation, lower fibrinogen concentrations, and increased insulin sensitivity and glucose metabolism. However, heavy alcohol consumption is associated with an increased risk of all types of strokes, especially, haemorrhagic intracerebral haemorrhage (11), as well as with hypertension, hypercoagulability, reduced cerebral blood flow, and an increased risk of AF (4).
    d. **Sleep-related breathing disorders:** obstructive sleep apnoea is a silent problem leading to multiple diseases such as hypertension, coronary artery disease, arrhythmias, ischemic stroke, metabolic disorders, cognitive impairment and more. Screening for sleep apnoea through a detailed history, including structured questionnaires, physical examination, and, if

indicated, polysomnography may be considered in people with a history of excessive daytime sleepiness, high body weight, narrowed airway and a family history of sleep apnoea.

e. **Air pollution:** Even though air pollution was not in the top ten potentially modifiable risk factors associated with acute stroke in the 32 countries, airborne particulate matters under 10 μm (PM10), 2.5 μm (PM2.5) and other toxic particulates have been connected to ischemic stroke. In nationwide studies, Korea and China found that both short-term and long-term exposure of ambient PM were associated with ardioembolic stroke and also increased stroke mortality (13,14).

8. Atrial fibrillation and extracranial carotid artery stenosis

   a. **Atrial fibrillation:** An estimate of an individual's risks for cardioembolic stroke after established diagnosis of atrial fibrillation (persistent or paroxysmal) is important. In most clinical practice, we use CHA2DS2-VASc score (15) to estimate the risk with 0 points corresponding to low risk (0.5%–1.7%/y), 1 point reflecting moderate risk (1.2%–2.2%/y), and ≥2 points indicating high risk (1.9%y–7.6%y) (16). AHA/ASA guidelines recommend long-term oral anticoagulant therapy with warfarin at a target INR of 2.0 to 3.0 for people with valvular AF at high risk for stroke and those with previous stroke or TIA. Direct oral anticoagulant (DOACs) can be used in nonvalvular AF patients to prevent or reduce the risk of stroke (4,7).

   b. **Extracranial carotid artery stenosis:** General screening for carotid artery stenosis in the general population is not recommended as not every carotid stenosis carries the same risk for future stroke. The best medical treatment with antiplatelet, screening for other treatable risk factors of stroke and lifestyle changes are suggested. Surgical intervention is still under debate for primary prevention (17). However, carotid endarterectomy (CEA) is strongly recommended in people with a TIA or nondisabling ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis (7).

In conclusion, it is evident that the risk of cerebrovascular disease is dependent on a multitude of risk factors. Yet, more than 80% of the global burden for stroke is attributable to modifiable risk factors. Therefore, if the general population can modify their lifestyle, diet and/or other behaviours, we should be able to better mitigate the associated risk factors, like atherosclerosis vascular risk factors, and reduce the occurrence of stroke and its associated risk of dementia.

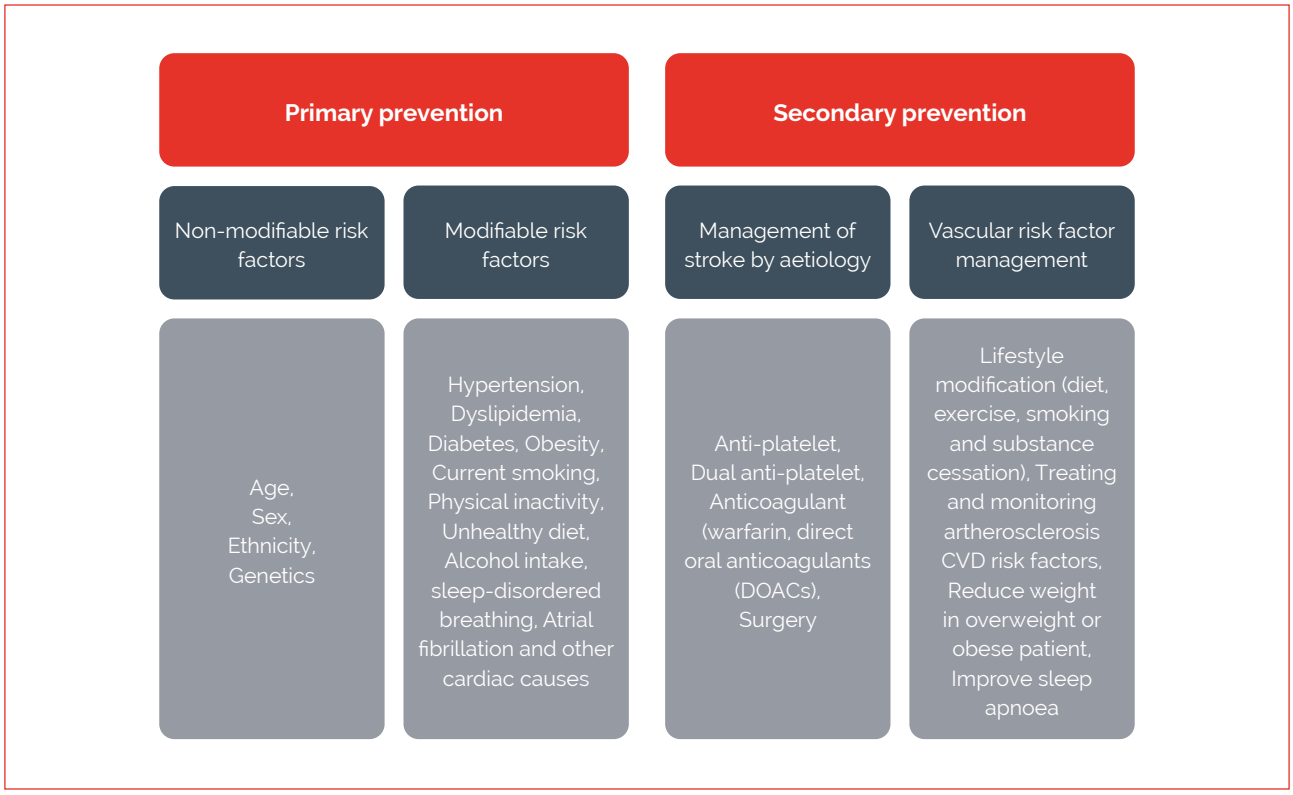

Figure 1. Summary of well-known risk factors for ischemic stroke in terms of both primary and secondary prevention.

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Expert essay

Post-stroke cognitive impairment: in search of a profile that may inform treatment

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Cerebrovascular disease, including clinically overt stroke and silent cerebrovascular disease, is an important contributor to cognitive dysfunction (1). Among stroke survivors, 44% will go on to develop some form of cognitive impairment with an estimated 10%–20% going on to develop dementia (2–4). The incidence of delayed onset post-stroke dementia ≥5 years after stroke is up to 9 times greater than the age-matched population (5). Several studies have demonstrated that even among people who suffer mild strokes (modified Rankin <3), up to 41% go on to develop mild cognitive impairment (6). Clinical outcomes are also poorer for stroke survivors who develop post-stroke cognitive impairment, including poorer physical outcomes, higher institutionalisation and higher mortality than non-PSCI stroke survivors (7,8). However, the focus of post-stroke care has traditionally been on physical disability, while screening for post-stroke cognitive impairment, which may develop in the acute stage or delayed until years after stroke, is often overlooked. Therefore, it is paramount to emphasise the importance of cognitive assessment of stroke survivors by stroke-clinicians. Reviews of studies have found significant heterogeneity related to the study setting (populations which include patients with minor strokes versus hospital-based), inclusion or exclusion of pre-stroke dementia, differences in diagnostic criteria and geographic regions (2,9). Hence, efforts to harmonise the methodologies of future studies are greatly needed to have a better understanding of post-stroke cognitive impairment, including cognitive and neuropathological markers, risk factors and mechanisms. This knowledge will better inform prognosis and guide evidence-based interventions using precision-medicine practices.

Risk factors, neuropathology, and mechanisms of post-stroke cognitive impairment

The risk profiles can be broadly categorised into demographics, cardiovascular risk factors, pre-stroke pathologies and acute stroke characteristics. Demographic factors such as increasing age and low education are consistently demonstrated to increase the risk (2,10). On the other hand, evidence of hypertension, diabetes mellitus, hyperlipidaemia, smoking, and atrial fibrillation as specific cardiovascular risk factors of post-stroke cognitive impairment, beyond being risk factors for ischemic strokes, are less consistent. A systemic review in 2009 found that diabetes and atrial fibrillation are significant predictors (2), while a recent study which harmonised data from 13 studies found that diabetes is strongly associated with post-stroke cognitive impairment while hypertension, smoking, and atrial fibrillation have weaker domain-specific associations (4).

The neuropathology of cerebrovascular disease which can be visualised on structural MRI is heterogenous and includes a combination of acute stroke lesions such as large territorial infarcts, multiple infarcts, strategic infarcts and brain haemorrhage, and chronic cerebrovascular disease lesions such as white matter hyperintensities (WMH), lacunes and microbleed (3). Given the key role of dementia-prone acute stroke lesions in causing post-stroke cognitive impairment, a recent study pooled data from 12 acute ischaemic stroke cohorts and reported a map of strategic infarcts associated with post-stroke cognitive impairment. Specifically, infarcts

in the left frontotemporal lobes, left thalamus, and right parietal lobe were strongly associated with PSCI (11). However, not all dementia-prone acute stroke lesions lead to post-stroke cognitive impairment, and brain resilience, which is defined as the overall capacity of the brain to recover from injury and to maintain its usual function, has been proposed to have a complex interplay with acute stroke lesions in influencing the risk (3).

Emerging evidence suggests that the risk is also driven by pre-existing brain atrophy and extent of chronic cerebrovascular disease in stroke survivors. Global cortical atrophy, which reduces brain reserve, has been shown to increase the risk of post-stroke cognitive impairment (12) and increase the range of cognitive domains impaired after stroke (13). Such global cortical atrophy may suggest concurrent Alzheimer's disease. The Stroke Registry Investigating Cognitive Decline (STRiDE) study showed that amyloid deposition is more frequently present in those with early-onset dementia (29.7%) after stroke than in those without (7.7%) (14). The presence and severity of white matter hypertensities, an imaging feature of cerebral small vessel disease, have also been shown to substantially increase the risk of dementia, functional impairment, stroke recurrence and mortality after ischaemic stroke in a recent systemic review of 71,298 ischemic stroke patients (15). Furthermore, findings from the STRiDE study showed that severe small vessel disease, as reflected by confluent white matter hyperintensities and/or multiple lacunes, are independent predictors of delayed onset dementia after stroke (16). Microbleeds, another silent cerebrovascular lesion which characterises tissue damage due to small vessel cerebrovascular disease or accumulation of amyloid in the vessels, are shown to be associated with increased risk of developing post-stroke cognitive impairment, with one recent study showing that risk increased by four times (17). The risk of post-stroke dementia also varies depending on the presence of chronic cerebrovascular pathologies and type of acute infarcts. In this regard, we recently found that the risk of post-stroke dementia was largest for stroke survivors with acute large subcortical infarcts (>15 mm) and concomitant periventricular white matter hyperintensities compared with patients with large subcortical infarcts and punctate/absent periventricular white matter hyperintensities (18). Therefore, profiling chronic cerebrovascular disease lesions in addition to acute stroke lesions in stroke survivors plays a critical role in informing the prognosis of post-stroke cognitive impairment and post-stroke dementia.

Future directions

Several clinical and neuroimaging factors have been identified as predictive of post-stroke cognitive impairment among stroke survivors. Therefore, to facilitate the screening of individuals at risk of delayed post-stroke cognitive impairment, risk scores that incorporate clinical and neuroimaging markers commonly adopted in clinics such as CHANGE have been developed to specifically identify stroke survivors at risk (19). However, it is important to note that the factors may differ in predicting acute or delayed onset, and therefore, a 'one approach fits all' characterisation of risk factors for all post-stroke cognitive impairment may not be justifiable. In addition to structural MRI, evaluation of white matter tract integrity using diffusion tensor imaging and imaging of blood brain barrier integrity will also be useful. Profiling each factor at the appropriate time point post-stroke to reliably predict the risk of post-stroke cognitive impairment will allow a precision medicine approach so that a personalised intervention can be applied at the right time to improve cognitive outcome. However, the large clinical and neuroimaging heterogeneity of risk factors and mechanisms highlights the difficulty of developing a consensus on the most reliable factors to inform clinicians who treat stroke survivors. Furthermore, many existing studies did not account for factors such as premorbid cognitive ability or resilience/reserve.

To address these inconsistencies, there have been international efforts to form consortiums with the aim to develop a standardised approach when pooling data from cohorts (11,20). One such effort is the Stroke and Cognition Consortium (STROKOG), which harmonises data from participants from different continents, so as to facilitate a better understanding of the determinants of vascular contributions to cognitive disorders and help improve the diagnosis and treatment of vascular cognitive disorders (20). Future research may also benefit from pooling of the international consortia to form larger datasets with harmonised study methodologies. The pooling of data across the world will further support the use of machine learning and artificial intelligence to better characterise the risk profiles of post-stroke cognitive impairment to help find patterns and trends which will support the development of individualised predictive models to inform a personalised multi-domain intervention.

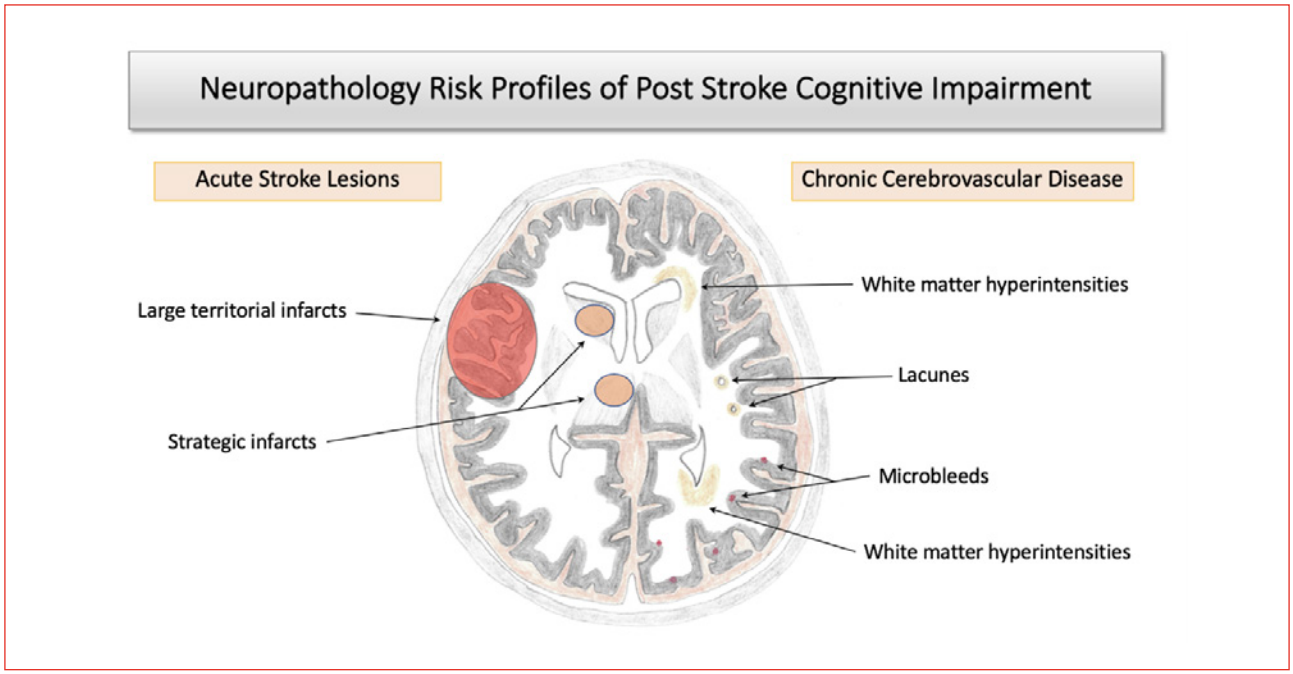

Figure 1. Illustration of brain vascular lesions of various size and location.

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Expert essay

Nutritional deficits in the differential diagnosis of dementia

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Both malnutrition and low levels of specific nutrients are associated with cognitive impairment and dementia in older adults. Malnutrition has been shown to contribute to the rapid decline in dementia. Most prevalent and significant deficiencies are vitamins B1, B9, B12 and D. Each of these has a specific proposed mechanism. Older people should be regularly screened for malnutrition and vitamin deficiencies. Prophylactic vitamin supplementation is not recommended and should be reserved only in cases of proven deficiencies. A well-balanced nutritional therapy based on the Mediterranean diet guidelines and oral nutrition supplements should be endorsed to all older people.

Introduction

The burden of malnutrition is heightened in older people with the process of ageing and has been correlated to cognitive decline and the risk of dementia. In addition to muscle loss and frailty, malnourished older people develop deficiencies in vitamins and minerals with a known metabolism linked to cognitive function. Therefore, clinicians should be aware of these nutritional deficits in both the assessment process and the treatment plan of older people at any stage of dementia (1).

Malnutrition in older adults and risk of dementia

Weight loss is the first identified criterion of malnutrition, and it has been directly linked with the severity of dementia in data across several countries. Prevalence of malnutrition has been reported to be up to 50% in people with Alzheimer's disease, especially in low- and middle-income countries. Dementia severity was also independently associated with muscle wasting in isolation of other risk factors and malnutrition was presented to be a strong predictor of disease progression and cognitive decline (2). This correlation can be explained by the different problems encountered during the stages of dementia and directly affecting food intake such as olfactory dysfunction, dyspraxia, agnosia and dysphagia (3).

Metabolism of vitamins and cognitive function

Consequently, the decrease in food intake and appetite loss observed during ageing and dementia is directly associated to deficiencies in micronutrients. The metabolism of these micronutrients, mainly B vitamins, has long been recognised to be linked to cognitive metabolism, and therefore to increased risk of dementia (4). The first vitamin of note is B12 or cobalamin, a very common one in older people due to decreased absorption. Its deficiency is well-established in association with elevated plasma levels of homocysteine, a risk factor of Alzheimer's disease (4). However, cross-sectional studies have been contradictory and a better correlation was established when serum levels of folate (vitamin B9) were taken into consideration (1). Since both vitamins are needed for the conversion of homocysteine to methionine, they share the metabolism of decreasing hyperhomocysteinemia. So far, trials on supplementation have been disappointing in preventing or delaying cognitive decline, but on the other hand, increased intake of folate and to a lesser extent B12 from food sources in observational studies have been linked to improving cognitive function and decreasing risk of Alzheimer's disease (5).

Another B vitamin that is linked to neurological problems is B1 or thiamine (6). Korsakoff syndrome, its well-known deficiency, shares some metabolic features in the brain with Alzheimer's disease. These features are directly linked in both cases with diminished glucose metabolism in the brain, a pathway dependent on thiamine. Reduced glucose metabolism has even been observed long before the person demonstrates significant clinical signs of dementia (6). Conversely, possible causes of deficiency have not yet been well-established. Besides alcoholism, thiamine deficiency from decreased intake is not very common due to flour fortification, but it is observed in older people in low-income countries where this fortification procedure is not mandated, and older people tend to consume fewer alternative protein sources of B1. To date, trials of thiamine supplementation have only been conducted in a small sample size generating non-conclusive results (6).

Besides B vitamins, vitamin D deficiency, which is very common in older people due to reduced sun exposure, among other factors, has implications for dementia onset and progression (7). With suggested mechanisms of amyloidosis in several areas of the brain and neurogenesis in the hypothalamus, cross-sectional and longitudinal studies have exhibited associations between low vitamin D levels and cognitive impairment (7). Since vitamin D supplementation is now commonly prescribed to treat deficiencies, intervention studies are starting to be conducted regarding its role in prevention and treatment of cognitive impairment (7).

Screening of nutrition status in diagnosing dementia

All these described metabolic pathways and mostly observational studies can be translated into practical implications in the diagnosis of dementia as well as its prevention and treatment in older adults. Screening for malnutrition should be done frequently in older adults at both community and hospital levels. Mini Nutritional Assessment® is a validated assessment tool for use in this population and is easy to use. It has well defined categories of risk for malnutrition and is comprised of questions related to food intake. These questions, if properly investigated, can determine if an older person is skipping meals or food groups, and consequently, is at risk for certain vitamin deficiencies (8). The next step would be to investigate these deficiencies through a biochemical assessment while focusing mainly on vitamin B12, folate and vitamin D. This in-depth nutrition assessment will add perspective to the differential diagnosis of dementia and guide the steps in its management (8).

Practical recommendations

Until now, recommendations on these specific vitamins' supplementation have only been proven efficient in delaying cognitive decline in case of deficiencies (4). Prophylactic supplementation should not be part of practice, but intake of these vitamins can be secured from a well-balanced diet. The Mediterranean dietary pattern based on consuming more fruits, vegetables and legumes, is particularly rich in these vitamin (except B12 that depends on animal sources of intake) in addition to other antioxidants and should be endorsed to older adults in order to prevent and even delay cognitive decline in the early stages of dementia (9).

In the case of malnutrition and decreased food intake, caloric and protein requirements cannot be met easily with a healthy diet alone. Oral Nutrition Supplements (ONS) may be added to the daily intake of an older adult with malnutrition or even who is at risk of malnutrition, and this, to enhance nutritional requirements. These ready-to-sip liquids in assorted flavours are easily consumed and incorporated into a daily routine. Their use is associated with increased weight, better quality of life and decreased mortality (10). An additional advantage of these oral nutrition supplements is their enrichment in the above-mentioned vitamins and omega-3, among other nutrients.

Risk of malnutrition and subsequent vitamin deficiencies are strongly correlated with cognitive decline. These established observations in many studies are now considered in the diagnosis of dementia by adding a well-defined screening of nutrition status. As for the prevention and treatment of dementia, healthy dietary patterns and fortified oral nutrition supplements are recommended for implementation in the management in cases of malnutrition. Larger intervention trials for specific vitamin supplementation are needed to establish more evidence-based recommendations on dosage and timing.

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Expert essay

How to evaluate the individual with ventriculomegaly on brain imaging

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As computer tomography (CT) and magnetic resonance imaging (MRI) are now widely available, brain scanning is easily integrated into the workup of those people presenting with cognitive complaints. In clinical practice, enlarged lateral ventricles are common. The Evans' index has been the most extensively used radiological marker of abnormal ventricular enlargement. It is defined as the ratio between the maximum diameter of the frontal horns of the lateral ventricles and the maximum inner diameter of the skull in the same section (Figure 1). Evans' index equal or over 0.30 is regarded as enlargement of lateral ventricles or ventriculomegaly. What is the clinical significance? What shall the clinician do if they encounter the appearance of enlarged ventricles on brain imaging? Some relevant information is provided below for reference.

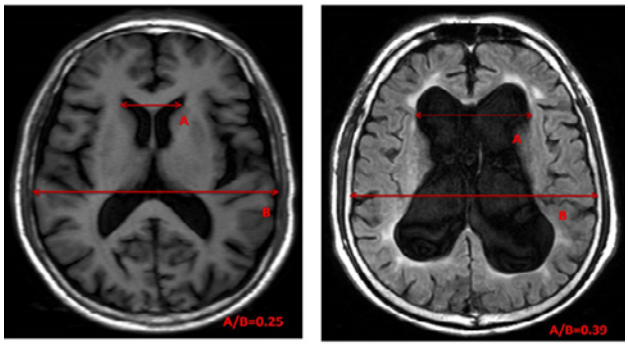

Figure 1. Left: Evens index = A/B < 0.3; Right: Evens index = A/B > 0.3.

Enlarged lateral ventricles can be caused by excessive cerebrospinal fluid (CSF), brain atrophy or both. Hydrocephalus is defined as excessive CSF in the ventricular system. CSF is produced through choroid plexus excretion, flow beginning from lateral ventricles to the third ventricle, the aqueduct of Sylvius and the fourth ventricle, enters the subarachnoid space through the median aperture and lateral apertures, finally absorbed into the venous sinuses of dura matter through arachnoid granulations following a fixed direction. Hydrocephalus can be divided into non-communicating/obstructive hydrocephalus and communicating hydrocephalus according to the presence of the obstruction in the CSF flow pathway or not. The former can lead into acute intracranial hypertension with headache, vomiting, and/or disturbances of consciousness. Therefore, obstructive hydrocephalus is seldom ignored and misdiagnosed. The latter with some known causes such as subarachnoid haemorrhage, meningitis and head trauma is called secondary hydrocephalus. Communicating hydrocephalus without known causes, often with normal intracranial pressure, is called idiopathic normal pressure hydrocephalus (iNPH). iNPH is a condition characterised by gait disturbance, cognitive impairment, and urinary incontinence. However, its onset is slow, and the condition may go undetected until a triadic syndrome is fully established (1). Enlarged ventricles may be caused by brain atrophy, of which the most common cause is Alzheimer's disease. Both hydrocephalus and brain atrophy can coexist, which makes an accurate diagnosis even more difficult.

Enlarged ventricles caused by obstructive or secondary communicating hydrocephalus can be treated with shunt surgery, with a good outcome result in many people, hence the importance of further workup. Response to shunting is less predictable in iNPH. That is why this essay will further explore its clinical manifestations and investigation.

The individual with enlarged ventricles but with no symptoms or signs should be followed up regularly (2).

Gait disturbances may be the first symptom: the person cannot walk as fast as before or keep up with fellow pedestrians. Some individuals may just complain of unsteadiness or dizziness. Upon examination, there may be more variable and shorter strides as well as a lower cadence. The feet cannot be raised to a normal height. A decreased stride length, decreased foot-to-floor clearance and a broad-based gait are typical features of gait abnormality in iNPH (3). Over time, the gait disturbance in iNPH develops three characteristics: small-step gait, magnet gait, and broad-based gait. Freezing gait may become obvious when individuals are walking in a narrow space, or when they change direction. Due to this gait pattern, people

with iNPH are often misdiagnosed with Parkinson's disease; however, they do not present with increased muscle tone as with most Parkinson patients. Gait can be evaluated by the 3-meter Timed Up and Go test (TUG), 10-metre walking test, dual task walking test and Gait Status Scale. TUG is the most frequently used (4): the suggested procedure is to have the individual stand up from a seated position and walk a distance of 3 metres as quickly and as safely as possible. After reaching a line indicating the 3-metre distance, the person turns 180 degrees, walks back to the chair, and sits down as quickly as possible. The time it takes from standing to sitting is recorded, a mean value of 16.5 seconds being the cut-off. TUG is also very useful in predicting responsiveness to the shunt operation. The time difference recorded on the TUG is calculated as (TUG time before spinal tap test – TUG time after spinal tap test or shunt surgery): the improvement of 5 seconds on the TUG at the spinal tap test is a highly accurate predictive factor for improvement of 10 seconds on the TUG 12 months after shunt surgery (5).

Cognitive impairment may be described as not being able to think as quickly as before, or the fact that figuring out a problem takes longer. Some people may describe their brain as being 'rusty' or something similar. iNPH is thus associated more with executive frontal lobe and attention deficits than with memory impairment. Psychomotor speed has declined, and attention and eventually working memory are impaired. The neuropsychological assessment can include short screening scales such as the Mini Mental State Examination (MMSE), or the Montreal Cognitive Assessment (MoCA; more sensitive than the MMSE for executive impairment). More specialised tests include the Frontal Assessment Battery (FAB), a short test designed to assess conceptualisation and abstract reasoning, mental flexibility, motor programming and executive control of action, resistance to interference, self-regulation and inhibitory control, as well as environmental autonomy. The Trail Making Test Part A (TMT-A) aims at evaluating psychomotor speed by connecting randomly located numbers in numerical order as quickly and accurately as possible. The TMT-B test which connects numbers and letters in an alternating sequence is partly included in the MoCA. Other more complex neuropsychological tests include the Stroop test, the Ray auditory verbal learning test (RAVLT), the Digit span, the Rey-Osterrieth complex figure test, the WAIS-III and the Grooved Pegboard Test.

Urge micturition or incontinence associated with an overactive bladder is characteristic of dysuria in people with iNPH. Due to common prostate hyperplasia, this symptom may be misinterpreted. The International Consultation on Incontinence Questionnaire is suggested for evaluation of urinary incontinence (6).

In the case of ventriculomegaly, particularly if supported by an abnormal Evans' index, it is important to evaluate the presence and severity of the key symptoms and signs (gait changes, cognitive decline and urine incontinence) of the iNPH triad, as the decision to undergo a shunt procedure requires a referral to a neurosurgical service for further assessment. This may include additional brain imaging and a CSF spinal tap test (7). This referral should be made by also factoring in the presence of advanced dementia and what is in the person's best interests.

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Conclusions

The essays contained in this Chapter demonstrate the importance of identifying vascular risk factors that contribute to the development of cognitive impairment and, subsequently, how this illness is managed. The distinctive perspectives converging on the same topic highlight the complexity of recognising symptoms and rendering an accurate diagnosis. These contributing risk factors are two-fold. They include non-modifiable ones, those out of your control, such as age, gender, ethnicity or genetics as well as modifiable ones, signalling the lifestyle choices you make and control, including smoking, level of physical activity, alcohol consumption or hypertension. For example, modifiable risk factors greatly contribute to the onset of stroke, which engenders possible long-term cognitive degeneration.

Malnutrition, or even a decrease in caloric intake, is another prevalent risk factor, leading to a deficiency in essential nutrients associated with cognitive impairment and dementia in older adults. This condition can be enhanced by taking fortified nutritional supplements that complement food intake and provide vitamin supplementation.

Finally, identifying iNPH at the earliest opportunity, for example when gait disturbance appear, may ward off further complications before cognitive deficits occur. As many of these factors are present at middle age, a preventive approach should be adopted. For example, in community-dwelling individuals of a mean age of 53 years, walking more than 7,500 steps a day, which is considered light physical activity and accessible to most older adults, was associated with higher total brain volume, equivalent to approximately 1.4 to 2.2 years less brain ageing (1).

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