Chapter 11
Cognitive Dysfunction After Intracerebral Hemorrhage, Vasculitis, and Other Stroke Syndromes

Eric E. Smith and José Andrés Venegas-Torres

Introduction

Cognitive impairment following stroke is predominantly related to the region of destroyed brain tissue, the capacity for accommodating the loss of function that results, and the degree of recovery. However, some of the variance in cognitive function after stroke is related to the mechanism of stroke. Most strokes result from brain ischemia, but up to 15 % may be due to subarachnoid (see Chap. 10) or intracerebral hemorrhage (ICH). Among the strokes resulting from brain ischemia, most are caused by hypertensive arterial disease, atherosclerotic disease, or cardiac disease. However, a minority may be caused by a wide range of less common arterial or hematologic diseases, including vasculitis, hypercoagulable states, and others. In some cases, these diseases may have their own effects on cognitive function independent of the presence of stroke, with their own tempo and characteristics. Here, we review the associations between cognitive function and ICH, and cognitive function and less common causes of ischemic stroke.

E.E. Smith, M.D., M.P.H. (✉)
Department of Clinical Neurosciences, Foothills Medical Centre,
Room C1212, 1403 29 Street NW, Calgary, AB, Canada T2N 2T9
e-mail: Eric.Smith@albertahealthservices.ca

J.A. Venegas-Torres, M.D.
Department of Clinical Neurosciences, Calgary Stroke Program,
University of Calgary, Foothills Medical Centre, Calgary, AB, Canada

Fig. 11.1 Acute intracerebral hemorrhage (ICH), appearing as a hyperdense (*bright*) lesion on computed tomography (CT) scan
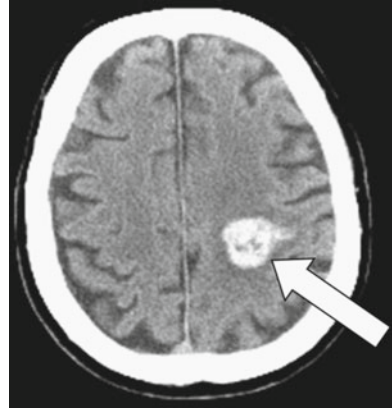
Intracerebral Hemorrhage

Etiology and Epidemiology

ICH results from rupture of blood vessels in the brain (Fig. 11.1) [1]. In some cases the blood may extend into the ventricles or, less commonly, the subarachnoid space. The annual incidence is 10–30 per 100,000 population, accounting for two million (10–15 %) of about 15 million strokes that occur worldwide each year. Although the age-specific incidence of ICH is stable or decreasing, probably due to better population control of hypertension, the absolute number of ICHs is expected to rise in the next decades because of aging of the population. Compared to ischemic stroke, the case fatality rate of ICH is much higher, with only 38 % of affected patients surviving the first year. Many survivors are left with significant residual disability.

Depending on the underlying cause of bleeding, ICH is classified as either primary or secondary [1]. Primary ICH, accounting for 78–88 % of cases, originates from the spontaneous rupture of small vessels damaged by chronic hypertension or cerebral amyloid angiopathy (CAA). Secondary ICH occurs in a minority of patients in association with vascular abnormalities (such as arteriovenous malformations and aneurysms), tumors, or impaired coagulation. However, ICH associated with anticoagulant medication is typically considered a form of primary ICH; for example, evidence suggests that warfarin-related ICH is associated with the same small vessel diseases, such as CAA, that cause primary ICH [2]. There are many potential causes of secondary ICH (see Table 11.1). Except for vascular malformations as a cause of ICH in younger patients, these secondary causes are rare. Younger patients with ICH should have angiography to rule out secondary causes.

The most common locations of ICH are the cerebral lobes (35 %), the basal ganglia (30 %), the thalamus (20 %), the brainstem (5 %), and the cerebellum (10 %) (Fig. 11.2) [3]. It is useful to discriminate between lobar and non-lobar locations of

Table 11.1 Primary and secondary causes of intracerebral hemorrhage (ICH)

Primary ICH
Hypertensive arteriolosclerosis
Age-related arteriolosclerosis
Cerebral amyloid angiopathy
Secondary causes of ICH
Vascular malformations
Arteriovenous malformation
AV dural fistula
Cavernous hemangioma
Hemorrhagic transformation of ischemic stroke
Related to arterial infarction
Related to venous infarction
Vasculitis
Moyamoya disease
Coagulopathy
Related to anticoagulant use
Related to thrombolytic use
Thrombocytopenia
Decreased synthesis of clotting factors (e.g., hemophilia, liver disease)
Increased consumption of clotting factors (e.g., disseminated intrasvacular coagulation)
Brain tumor
Aneurysm
Ruptured saccular aneurysm
Ruptured mycotic aneurysm
Related to sympathomimetic drug use
Amphetamines
Cocaine
Phenylpropanolamine
Ephedrine
Trauma

primary ICH, because the associated causes and risk factors differ by location. Lobar ICH may be caused by either CAA or hypertensive arteriosclerosis, while non-lobar primary ICH is almost exclusively caused by hypertensive arteriosclerosis. This is because CAA affects the cortical and leptomeningeal arteries but not the arteries penetrating into the substance of the brain, while most hypertension-related ICHs occur at or near the bifurcation of small penetrating arteries that originate from the major branches of the circle of Willis. Accordingly, hypertension is a stronger risk factor for non-lobar ICH than lobar ICH, while conversely the presence of one or more apolipoprotein E epsilon 4 (apoE ε4) alleles, associated with the presence of CAA, is a stronger risk factor for lobar ICH than non-lobar ICH [4, 5]. Other risk factors for ICH include age, male sex, cigarette smoking, low (not high) serum cholesterol levels, and Hispanic, African, or Asian racial origin [1, 6].
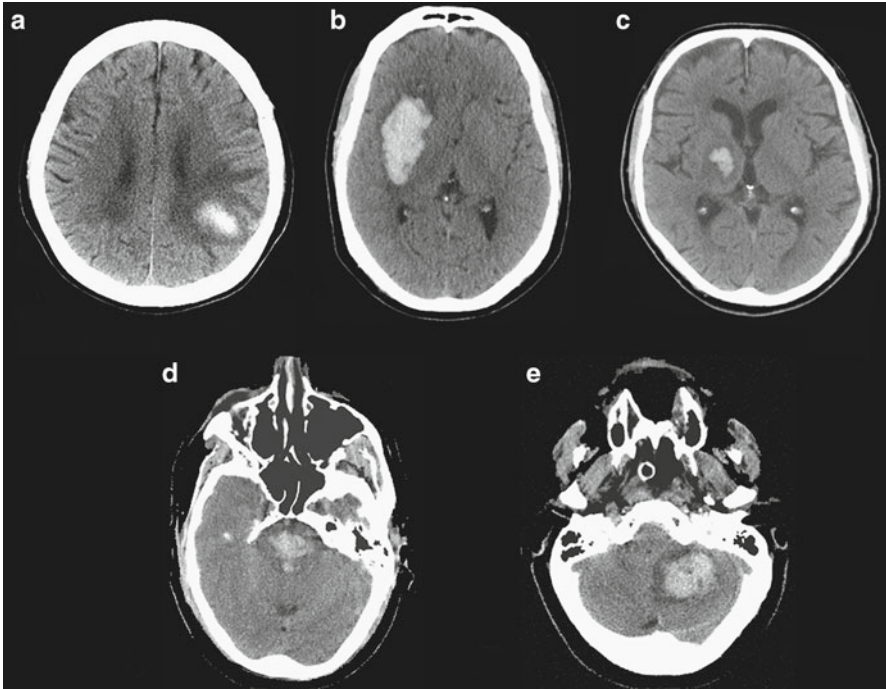
Fig. 11.2 Common locations of ICH: (**a**) cerebral lobe (lobar), (**b**) basal ganglia (putamen), (**c**) thalamus, (**d**) brainstem, (**e**) cerebellum

Cognitive Symptoms and Signs in Acute ICH

Cognitive symptoms in acute ICH depend on the location of bleeding. ICH may cause neurological dysfunction by local destruction of tissue, local mass effect with compression of tissue, potential toxic effects of iron or other molecules found in coagulating blood, or increased intracranial pressure caused by mass effect or obstruction of the ventricular system.

Small- to medium-size ICHs that do not increase intracranial pressure typically present with focal neurological symptoms reflecting the site of origin of the ICH. These may include hemiparesis, hemiplegia, aphasia (resulting from ICH in the left perisylvian cortex), or neglect or visual–spatial difficulty (most commonly resulting from ICH in the parietal cortex). ICH in the thalamus may also present with these "cortical" signs of aphasia (left thalamus) or neglect (right thalamus). ICH in the basal ganglia is usually associated with more prominent motor signs, such as hemiparesis, than cognitive signs; however, survivors of basal ganglia ICH often have cognitive deficits as well (discussed in the subsequent section: "Cognitive Consequences of ICH").

Larger ICHs that cause increased intracranial pressure, or ICHs in the brainstem or thalamus that affect the reticular activating system or its connections in the thalamus, often present with depressed level of consciousness in addition to other signs. In many cases the level of consciousness is significantly depressed and confounds the ability to assess other aspects of cognition. Depressed level of consciousness at presentation is more common in ICH than ischemic stroke; however, there are no signs or symptoms that reliably distinguish between ICH and ischemic stroke.

Delirium is a frequent complication in the first several weeks following ICH. Many factors may contribute to the risk of delirium; among them are the size of the ICH and the presence of intraventricular hemorrhage. Neurological toxic effects of blood break-down products may also contribute. In animal studies, experimental ICH is followed by extensive brain inflammation that worsens cognitive and motor function. The significance of post-ICH secondary injury in humans remains unclear, although post-ICH edema can be detected using neuroimaging. Patients with ICH have as much as a fivefold increased odds of post-stroke cognitive impairment and delirium in the first few weeks compared to patients with ischemic stroke [7].

Cognitive Consequences of ICH

ICH is the most severe form of stroke. Most survivors will have residual disabilities, and cognitive symptoms are common.

Dementia frequently accompanies stroke, both ischemic and hemorrhagic. According to a recent systematic review, about one in ten patients have dementia before their first stroke and one in ten develop new dementia after their first stroke. The risk of post-stroke dementia is higher in ICH than in ischemic stroke, reflecting the greater severity of ICH [8]. Risk factors for dementia following ICH specifically, as opposed to stroke in general, have not been well defined. Based on studies done in consecutive patients with either ischemic stroke or ICH, the expected risk factors for dementia post-ICH might be higher initial stroke severity, advanced age, left hemisphere origin, aphasia, and prior history of stroke or dementia [8].

A history of dementia preceding ICH is seen in 15–23 % of patients [9, 10]. Preexisting dementia is associated with increasing age, female gender, low educational level, severity of cerebral or temporal lobe atrophy, previous stroke or transient ischemic attack, severity of leukoaraiosis, diabetes, atrial fibrillation, and arterial hypertension. The high prevalence of pre-ICH dementia suggests that dementia may be more common in persons who develop ICH than other similar-aged persons, although this has not been proven in an epidemiologic study. Patients who develop ICH could be at risk for dementia, independent of the ICH, because of shared risk factors. Hypertensive arteriolosclerosis and CAA, the most common causes of ICH, also cause brain microscopic infarction and ischemic white matter demyelination (also known as leukoaraiosis) that contribute to the risk of dementia. Leukoaraiosis is frequently seen in the brains of persons with ICH and is associated with pre-ICH dementia (Fig. 11.3) [10, 11]. CAA may be accompanied by
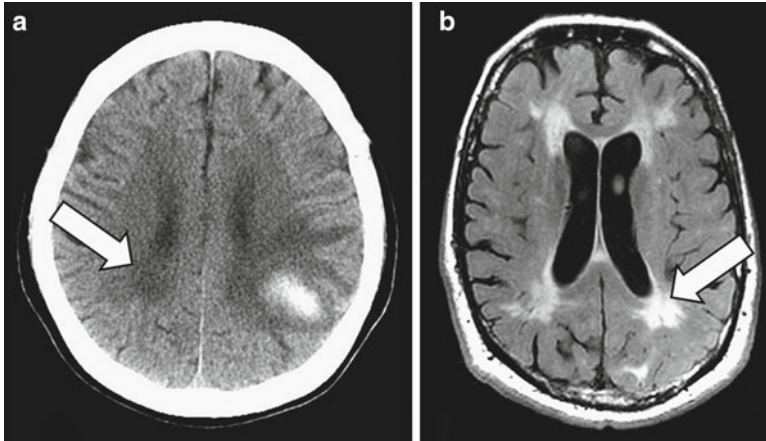
Fig. 11.3 Leukoaraiosis appears on CT as periventricular white matter hypodensities in this patient with a left parietal lobar ICH (**a**, *arrow*), and on T2-weighted MRI as hyperintensities (different patient) (**b**, fluid attenuated inversion recovery [FLAIR] sequence, *arrow*)

Alzheimer's pathology, although fewer than half meet pathological criteria for Alzheimer's disease [12].

Milder forms of cognitive impairment are even more common than dementia following stroke [13]. As a screening test for cognitive impairment, the Montreal Cognitive Assessment tool (MoCA) is more sensitive at detecting milder forms of cognitive impairment than the Mini-Mental State Examination (MMSE) [14]. However, there are very limited data on the prevalence of mild cognitive impairment following ICH specifically.

The pattern of deficits on neuropsychological testing in ICH patients depends on the location and severity of the hemorrhage, the ability of the brain to accommodate the cerebral damage (which in turn depends on the overall health of the brain, including the degree to which the brain is damaged by other effects of small vessel disease such as leukoaraiosis), and the degree of neurological recovery. Therefore, the resulting neuropsychological syndrome may reflect a combination of focal deficits related to the site of origin of the ICH, as well as global deficits as a consequence of more widespread neuronal injury caused by globally raised intracranial pressure, for example. Although it is useful to consider the neuropsychological deficits from ICH in terms of site of origin, it also must be recognized that the ICH may have extended from the site of origin to involve neighboring white matter or other brain structures.

Patients with lobar brain hemorrhages are expected to display abnormalities on neuropsychological testing that reflect a decline in function in the areas affected by the hemorrhage. For example, a patient with a left posterior superior temporal ICH may show symptoms of Wernicke's aphasia.

Patients with the more common non-lobar brain hemorrhages may display a variety of deficits. Non-lobar hemorrhages most commonly affect subcortical brain regions—the putamen, head of the caudate nucleus, and thalamus—that communicate widely with the frontal lobes via feedback loops to regulate thought and mood.

The striatum (caudate nucleus and putamen) is the main input structure of the basal ganglia. Given the connections between the striatum and the convergent loops related to the major cortical areas of the brain, damage to the striatum may result in a multitude of deficits pertaining to motor, oculomotor, cognitive, associative, and limbic functions. Indeed, ICH in the basal ganglia has been associated with poor performance in multiple cognitive domains including language, attention, memory, visuospatial processing, and executive function abilities, with many patients showing impairment in multiple domains [15].

Patients with ICH in the putamen may have impairments in executive function, visuospatial function (including neglect), apraxia, and aphasia. On the Wisconsin Card Sorting Test (WCST), patients with putaminal ICH have been shown to have impaired mental set shifting with disrupted concept formation or problem solving (the inability to comprehend the possible sorting rules) and perseveration (the inability to flexibly shift attention and response preparation from one set of rules to another) [16]. Unilateral spatial neglect can be detected in up to half of patients [17, 18]. Motor apraxias may occur in 20–40 % [19]. Aphasia may occur, and is related, at least in part, to extension of the hemorrhage into adjacent white matter pathways [20]. Extension into the deep frontal and anterior periventricular white matter causes decreased fluency, while extension to the deep temporal white matter causes impaired word comprehension. Hemorrhage extension into both the anterior and posterior periventricular white matter may cause a global aphasia. Extension more laterally into the region of the external capsule may cause conduction aphasia [21, 22]. Buccofacial oral apraxia often accompanies the aphasia [23].

Patients with ICH in the head of the caudate nucleus may have impairments in executive function, short-term and long-term memory, apathy, or aphasia [24–26]. Impaired mental set shifting and perseveration may be seen on the WCST [24]. One study suggests that the most prominent impairments are in short-term memory, long-term memory, and verbal fluency [24]. Aphasia following hemorrhage restricted to the caudate is rare, but is not infrequent when the hemorrhage also involves the neighboring white matter tracts [26].

Patients with ICH in the thalamus may have impairments in executive function, short-term and long-term memory, apraxia, aphasia, or neglect. Thalamic aphasia may be seen in lesions located in the dominant hemisphere and is characterized by fluent speech with paraphasias, perseveration, and lack of spontaneous speech but relatively preserved comprehension and repetition. Unilateral spatial neglect is more common with right-sided lesions, and often improves clinically over time [27].

In sum, a wide variety of neuropsychological deficits may be detected in survivors of ICH. Patients with small to moderate-sized lobar ICHs may have focal neuropsychological deficits related to the site of injury, while patients with larger ICHs or ICHs originating in non-lobar subcortical structures typically have deficits in

multiple domains, including aspects of executive function, visuospatial function, aphasia (for dominant hemisphere lesions), and neglect (for nondominant hemisphere lesions). In patients with subcortical ICHs, particularly those originating in the putamen and caudate nucleus, the cognitive deficits may predominantly reflect injury to adjacent structures including white matter pathways, rather than damage to the putamen or caudate themselves. The cognitive profiles of ICH are not distinct enough to discriminate ICH from ischemic stroke based on neuropsychological testing alone, although patients with ICH have been described to have somewhat more prominent problems with higher-level perceptual functions [25].

Diagnosis and Medical Management

There are no signs or symptoms that reliably distinguish between ICH and ischemic stroke; therefore, neuroimaging is needed to distinguish between the two [28]. Computed tomography (CT) shows similar sensitivity to magnetic resonance imaging (MRI) for acute hemorrhage and is often the initial investigation of choice. Medical management includes supportive care, control of excessively high blood pressure, lowering intracranial pressure if necessary, provision of hydration and nutrition, and prevention and treatment of medical complications such as seizure, deep venous thrombosis, and infection [28]. Severely affected patients may require intubation and mechanical ventilation. Limitation of care or palliation may be appropriate in severely affected patients with little hope of survival or meaningful quality of life [29, 30]. Surgical removal of the hematoma is often performed for patients with secondary ICH, cerebellar ICH, or with lobar ICH and clinical deterioration, and less commonly for patients with non-lobar-hypertensive ICH [31]. Expansion of the ICH occurs in up to 40 % of patients within 24 h of hospital presentation and may be lessened by good blood pressure control [32]. Trials of hemostatic therapies have not shown a clinical benefit despite demonstration of a modest reduction in ICH growth [33].

The risk of recurrent hemorrhage is approximately 2 % per year for non-lobar ICH and 5–10 % per year for lobar ICH. Recurrences are more frequent when blood pressure is poorly controlled. Among lobar ICH patients, risk factors for recurrence include prior symptomatic ICH, a greater number of MRI-defined microbleeds, the presence of one or more apoE ε(epsilon)2 or ε(epsilon)4 alleles, and the probable presence of underlying CAA. Risk factors for recurrence in patients with proven CAA are the same but also include the use of aspirin and the presence of leukoaraiosis [10, 34, 35].

Rational steps to prevent recurrence include blood pressure reduction and cessation of smoking and alcohol use [28]. However, these secondary prevention strategies are of unproven benefit with the exception that data from a randomized trial support an effect of blood pressure reduction [36, 37].

Whether better supportive care leads to improved cognitive outcomes is currently not known. There are no proven therapies for cognitive rehabilitation that are

Fig. 11.4 Microbleeds, evident as small *black dots* on MRI T2*-weighted gradient-recalled echo (GRE) sequence. The *white arrow* points to the largest microbleed
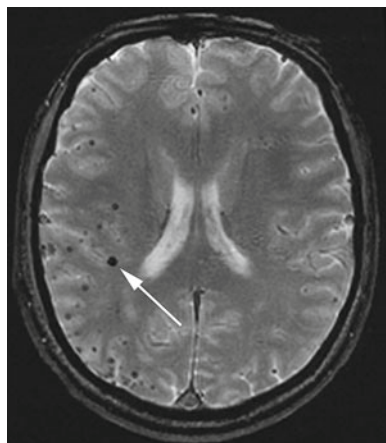
specific to ICH. Therefore, cognitive rehabilitation in ICH should follow the same principles as for ischemic stroke. This may include pharmacotherapy for depression or apathy. In our experience, stimulants such as methylphenidate may be used in ICH patients provided that blood pressure is monitored and controlled to avoid the risk of hypertension.

Brain Microbleeds

Microbleeds represent small (usually less than 5 mm) prior asymptomatic brain hemorrhages. Histopathologically, they appear as areas of perivascular hemosiderin deposition [38]. The hemosiderin molecule contains iron atoms derived from the breakdown of hemoglobin from red blood cells that previously leaked into the tissue. After deposition, the hemosiderin molecules remain in location indefinitely. Therefore the hemosiderin deposits across the brain represent the cumulative distribution of all the small hemorrhages experienced during the patient's life. These hemosiderin deposits are visible pathologically but may be overlooked because of their small size (usually 5 mm or less, and often as small as 1–2 mm). The deposits cannot be visualized on CT or on conventional MRI sequences but can be seen as "microbleeds" on specialized MRI sequences—T2*-weighted gradient-recalled echo (GRE) or susceptibility-weighted imaging (SWI)—where they appear as small dark round (i.e., hypointense) foci [39] (Fig. 11.4).

Microbleeds are a common finding in asymptomatic elderly, being present in at least 5–10 % of persons over the age of 60 [40]. However, the prevalence is much higher in persons with ischemic stroke (20–30 %) or ICHs (50–70 %). Microbleeds are a sign of cerebral small vessel disease, and when seen in large numbers, are most commonly associated with either poorly controlled hypertension or CAA. When

multiple and restricted to the cerebral cortex or subcortical junction, without involvement of subcortical structures such as the basal ganglia, they are highly suggestive of the pathological presence of CAA (see also the subsequent section: "Cerebral Amyloid Angiopathy") [41].

Previously, microbleeds were considered too small to directly affect brain function. More recently, this assumption has been questioned because of emerging evidence that microbleeds may be associated with cognitive impairment. For example, a case–control study done in patients seen in a neurovascular clinic found that executive dysfunction was more frequent in 25 patients with microbleeds compared to 30 controls without microbleeds, matched for stroke type, stroke location, and the extent of MRI white matter lesions [42]. In this study, executive dysfunction was defined as poor performance on two or more of the following tests: word fluency, Stroop, trail making, WCST, or Weigl Sorting Task. The stroke patients with executive dysfunction were more likely to have microbleeds in the frontal lobes and basal ganglia [42]. Microbleeds are frequently seen in persons with vascular dementia, but are also seen in up to 20 % of patients with mild cognitive impairment or clinically probable Alzheimer's disease [43–50]. Microbleeds have been associated with worse cognitive performance in adults without diagnosed neurological diseases [51–53].

However, caution is warranted before ascribing cognitive symptoms to the direct effects of microbleeds. Microbleeds may be merely a sign of an underlying cerebral small vessel disease causing cognitive dysfunction by mechanisms other than bleeding. For example, both hypertensive arteriopathy and CAA are associated with microbleeds but also cause microscopic infarctions that, in contrast to microbleeds, cannot be detected on MRI. Further studies are needed to clarify whether microbleeds affect brain function directly, or are merely an associated finding.

Cerebral Amyloid Angiopathy

CAA is caused by deposition of amyloid, a protein aggregate, in the media and adventitia of small arteries of the brain [54]. In most cases the amyloid is beta-amyloid, derived from the abeta protein. In some rare autosomal dominant hereditary diseases, the amyloid is derived from other proteins including transthyretin (in transthyretin amyloidosis), cystatin C (Icelandic familial dementia), or BRI (British familial dementia) [55]. CAA is most commonly clinically recognized as a cause of approximately half of lobar ICHs. However, the spectrum of clinical presentations of CAA also includes small sulcal subarachnoid hemorrhages, vasculitis, and transient neurological symptoms, and there is increasing evidence that CAA is a frequent contributor to the risk of dementia.

Arteries affected by amyloid deposition have thickened walls, fibrin deposition within the wall, and loss of wall integrity including circumferential cracking (a "vessel within a vessel" appearance) [54]. There may be perivascular hemosiderin deposits indicating leakage of red blood cells through the arterial wall [56].

Pathologically, the presence of amyloid may be diagnosed by the characteristic apple-green colored birefringence seen when affected arteries are stained with Congo red and then viewed under polarized light. An alternate means of pathological diagnosis is to identify the amyloid protein using an immunohistochemical stain.

Sporadic non-inherited CAA caused by beta-amyloid is a common age-associated pathology [57]. As with Alzheimer's disease, the prevalence of CAA is highly age-dependent and increases exponentially with increasing age. Some degree of CAA is seen in more than 40 % of persons over 80 [58]. In many cases, affected persons appear asymptomatic, although increasing evidence suggests that CAA is an important under-recognized contributor to the risk of dementia.

The common sporadic CAA is caused by aggregation of abeta into beta-amyloid with deposition in the vascular media. Abeta is derived from proteolytic processing of the amyloid precursor protein by beta-secretase and gamma-secretase. After formation, abeta can have several fates including aggregation into beta-amyloid with deposition in the arterial wall or brain parenchyma, proteolytic cleavage by enzymes such as neprilysin or insulin-degrading enzyme, or clearance from the brain via a perivascular interstitial fluid drainage pathway [59]. Aggregation of abeta with deposition as beta-amyloid may result from an imbalance between production and clearance of abeta [60]. Vascular beta-amyloid deposits are almost exclusively restricted to the leptomeningeal and cortical arteries.

The beta-amyloid seen in CAA is the same beta-amyloid that is the main constituent of the neuritic plaques seen in Alzheimer's disease. Indeed, the frequency and severity of Alzheimer's pathology is higher in the brains of persons with CAA than persons without [12]. CAA and Alzheimer's pathology may be conceived as being situated on the opposite ends of a spectrum, with some patients predominantly exhibiting vascular amyloid deposition (i.e., CAA) with increased risk of lobar ICH, and other patients predominantly exhibiting parenchymal amyloid deposition (i.e., Alzheimer's pathology) with increased risk of Alzheimer's type dementia.

The cause of nonhereditary beta-amyloid CAA is unknown. Other than age, the only other known risk factor is the presence of one or more apoE ε(epsilon)4 alleles [12]. Patients with one or more apoE ε(epsilon)2 alleles have more severe vasculopathic changes and may be at increased risk for ICH [61, 62]. Lowering of blood pressure and avoidance of antithrombotics and anticoagulants are reasonable steps to reduce the risk of recurrence.

Clinically, CAA is best recognized as a cause of approximately half of lobar ICHs in developed countries where there is good treatment of chronic hypertension. The hemorrhages may occur in any brain lobe, but have a predilection for posterior brain regions including the occipital lobe and posterior temporal and parietal lobes [63]. In about half of the cases of pathologically proven CAA-associated ICH, the lobar ICH is accompanied by one or more lobar microbleeds (Fig. 11.5) [41]. The presence of microbleeds in other locations not involved with vascular amyloid, such as the thalamus, basal ganglia, or brainstem, is not consistent with CAA and should prompt consideration of other causes such as hypertensive arteriolosclerosis. Diagnostic criteria for clinical research, termed the Boston criteria, discriminate
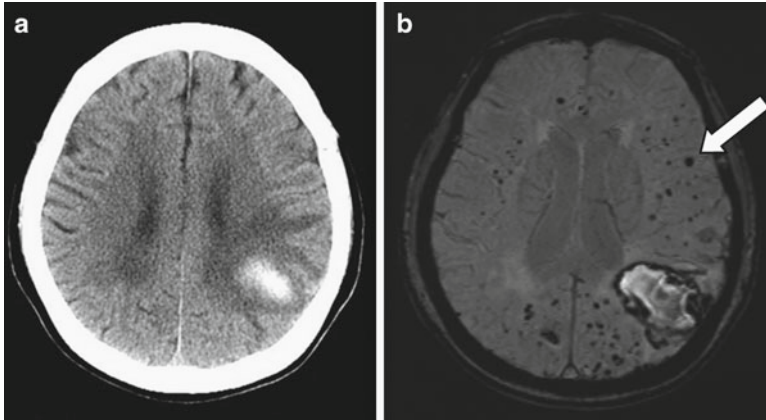
Fig. 11.5 Cerebral amyloid angiopathy (CAA). In this 70-year-old woman with left parietal lobar ICH (**a**, CT scan), MRI susceptibility-weighted imaging reveals dozens of small hypointensities indicating lobar microbleeds (**b**, *arrow*) not apparent on CT scan, consistent with probable CAA

Table 11.2 Boston criteria for diagnosis of cerebral amyloid angiopathy (CAA)-related ICH

Definite CAA	Full postmortem examination showing severe CAA
Probable CAA with supporting pathology	Pathologic tissue (evacuated hematoma or cortical biopsy) showing
	• Lobar ICH with some degree of CAA
	• Absence of other diagnostic lesion
Probable CAA	Clinical data and MRI or CT demonstrating
	• Multiple hemorrhages restricted to lobar regions or a single lobar hemorrhage with additional evidence of superficial siderosis
	• Age ≥55 years
	• Absence of other cause of hemorrhage or superficial siderosis
Possible CAA	Clinical data and MRI or CT demonstrating
	• Single lobar hemorrhage, or focal or disseminated superficial siderosis
	• Age ≥55 years
	• Absence of other cause of hemorrhage or superficial siderosis

These criteria were validated against autopsy data [41] and were recently modified to include incorporate evidence of superficial siderosis on MRI. Superficial siderosis is an MRI finding indicative of past bleeding in the subarachnoid space adjacent to the cortex or in the superficial cerebral cortex [65]

between *probable* and *possible* CAA based on presentation with lobar ICH and the presence or absence of accompanying lobar hemorrhages or microbleeds, without identifiable alternate causes (Table 11.2) [41]. Positron emission tomography (PET) with Pittsburgh Compound B or other beta-amyloid ligands will identify vascular beta-amyloid as well as parenchymal beta-amyloid, and could therefore be useful to confirm beta-amyloid deposition [64].

There are several less common presentations of CAA. Some patients present with vasculitis or perivascular inflammation and signs of patchy focal or multifocal edema in the periventricular white matter or juxta-cortical white matter, often involving the temporal or parietal lobes [66]. These patients may have a subacute cognitive decline, headaches, seizures, or focal neurological deficits such as hemiparesis. In some cases, the clinical course may be that of a rapidly progressive dementia. Neuroimaging shows brain edema, usually without infarction. In contrast to chronic white matter lesions, which are also common in CAA, the white matter lesions seen in CAA-associated vasculitis are not associated with atrophy but rather exhibit swelling and mass effect. When the edema is very focal, it may be mistaken for a low-grade tumor. There are usually multiple lobar microbleeds, although we have also seen pathologically proven cases without microbleeds. The cerebrospinal fluid often exhibits increased protein and sometimes a lymphocytic pleocytosis, but may also be normal. The diagnosis of CAA with vasculitis may be suspected on clinical and radiological grounds, but can only be definitively proven by biopsy. Immunosuppressive therapy, for example with steroids, can produce a dramatic clinical and radiological improvement in up to two-thirds of patients. Responders may stay in remission for years without need for chronic immunosuppression [66].

CAA is an important contributor to the risk of dementia, even in the absence of lobar ICH and accounting for the effects of accompanying Alzheimer's pathology. In the population-based Medical Research Council-Cognitive Function and Aging Study (MRC-CFAS) autopsy study, CAA accounted for 7 % of the risk of dementia, controlling for Alzheimer's disease pathology [67]. Similarly, another population-based study showed that for a given severity of Alzheimer's pathology, a higher degree of CAA was associated with worse performance on a global cognitive test [68].

The cognitive impairment seen in cerebral amyloid-angiopathy that is independent of hemorrhagic stroke is probably caused by brain ischemia. CAA is associated with a high burden of periventricular white matter demyelination [10], presumably on an ischemic basis, and small cerebral infarctions. Disturbed blood flow regulation with impaired vasodilation might play a role in generating these small infarctions [57].

There is limited information on the pattern of cognitive deficits that can be attributed to CAA, independent of the effects of lobar ICHs and coexisting Alzheimer's pathology. Based on the association between CAA and subcortical white matter lesions, deficits may be expected to include those associated with white matter disease, including poor performance on timed tests. However, cortical microscopic infarctions and microbleeds could produce signs of cortical dysfunction dependent on the location and severity of the pathological changes. A prospective cohort study with brain autopsy found that more severe CAA was correlated with worse performance on the symbol digit modalities test and a test of episodic memory, controlling for the amount of Alzheimer's pathology and in the absence of ICHs [69]. This poor performance on a timed test influenced by visual perception may reflect a combination of the subcortical ischemic white matter demyelination and predilection for the posterior parietal lobe and occipital lobe that are seen in cerebral amyoid angiopathy.

In summary, three potential contributing factors must be considered when evaluating cognition in a patient with probable CAA: (1) the effects of lobar ICH, if one has occurred; (2) the effects of accompanying Alzheimer's pathology, which may or may not be present; and (3) the effects of CAA independent of either lobar ICH or accompanying Alzheimer's pathology, which are presumably mediated by brain ischemia. The neuropsychological evaluation should therefore include tests sensitive to the cortical deficits expected based on the lobar ICH location, tests sensitive to the pattern of impaired memory retrieval seen in Alzheimer's disease, and tests sensitive to the impairments in psychomotor processing speed and executive dysfunction that may be seen with subcortical ischemic white matter disease.

Other Less Common Causes of Ischemic Stroke

The common causes of ischemic stroke are arterial disease related to hypertension and atherosclerosis, or cardiac disease related to coronary heart disease or atrial fibrillation. A substantial number of ischemic strokes are cryptogenic, which is defined as having no diagnosable cause. Other determined causes of stroke are rare. A comprehensive discussion of all uncommon causes of stroke is outside the scope of this chapter. Instead, we will highlight selected less common causes of stroke where cognitive impairment may be a prominent feature.

Cerebral Autosomal Dominant Arteriopathy with Subcortical Ischemic Leukoencephalopathy

Cerebral autosomal dominant arteriopathy with subcortical ischemic leukoencephalopathy (CADASIL) is a rare genetic cause of stroke, migraine, and vascular dementia [70]. The disease is caused by mutations of the NOTCH3 gene, which encodes the Notch3 receptor. Small arteries become thickened and fibrosed. Electron microscopy shows granular osmiophilic material adjacent to the vascular basement membrane, which is pathognomonic for the disease. Symptoms are limited to the central nervous system (CNS), even though arteries outside the brain are affected, in addition to those within the brain. Neuroimaging reveals multiple lacunar infarcts in the basal ganglia, thalamus, and white matter, along with extensive white matter demyelination (Fig. 11.6). Typically, the disease begins with migraine with aura in the victim's late 20s, lacunar strokes occur in their 40s, and vascular cognitive impairment and dementia occur in their 40s and 50s [71]. The diagnosis can be made by genetic analysis, or by skin or muscle biopsy with electron microscopy to identify the characteristic vascular changes with granular osmiophilic material.

CADASIL is an instructive disease because it is the prototypical example of a pure subcortical ischemic dementia. Because CADASIL patients develop dementia
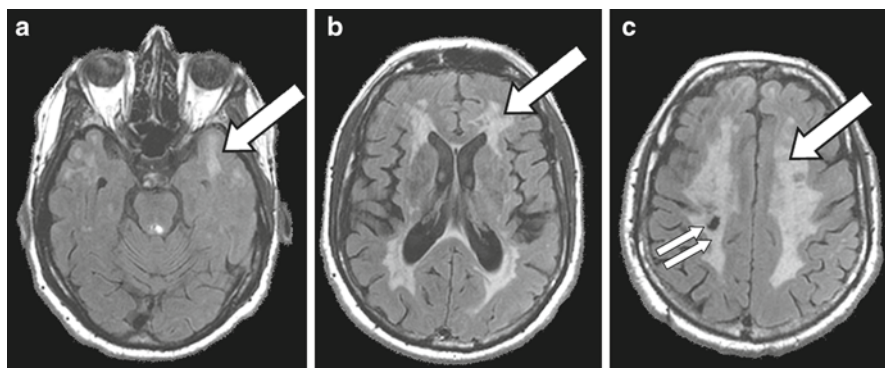
Fig. 11.6 Cerebral autosomal dominant arteriopathy with subcortical ischemic leukoencepha-lopathy (CADASIL): a 41-year-old man with CADASIL confirmed by genetic testing. The MRI FLAIR sequence shows extensive white matter T2-hyperintensities (**a–c**, *arrows*), including hyperintensities in the anterior temporal white matter (**a**) that are characteristic of CADASIL com-pared to other white matter diseases, and a lacunar infarct in the right corona radiate (**c**, *double arrow*)

at an early age, the cognitive profile of CADASIL is uncomplicated by other late-life pathologies of dementia such as Alzheimer's disease. In the earlier stages, CADASIL patients may display poor performance on neuropsychological tests sensitive to executive dysfunction including the Trail Making Test and tests of ver-bal fluency [72, 73]. As the disease progresses, more global cognitive impairments are seen, including memory. Apathy is a prominent neuropsychiatric symptom [74]. A randomized placebo-controlled trial of the acetylcholinesterase inhibitor done-pezil showed that treated patients had modest improvements on the Trail Making Test but no improvement in the global cognitive endpoint compared to the placebo group [75].

Vasculitis

CNS vasculitis is caused by vascular or perivascular inflammation. Pathologically, lymphocytic infiltration of the vascular wall or perivascular tissue is seen, with microglial activation. The inflammation may be idiopathic and isolated to the CNS, or may occur in the context of a systemic inflammatory disorder. CNS inflamma-tion, of either proven or suspected vascular origin, has been reported in polyarteritis nodosa, Churg–Strauss vasculitis, systemic lupus erythematosis (SLE), sarcoidosis, Wegener's granulomatosis, rheumatoid arthritis, Sjögren's syndrome, Behcet's disease, temporal arteritis, thromboangiitis obliterans (Buerger's disease), Kawasaki's syndrome, infections (particularly fungal infections causing basal men-ingitis), and other conditions. Generally, CNS vasculitis is a rare complication of

these systemic diseases. Diagnosing CNS vasculitis is challenging because it is rare and has many nonspecific manifestations. The literature on CNS vasculitis is often difficult to interpret because of changing perceptions and nomenclatures, with lack of pathological confirmation in many suspected cases.

The most common type of CNS vasculitis is primary angiitis of the CNS, also called isolated CNS angiitis [76]. Because giant cells are sometimes seen pathologically, this form of vasculitis has also been termed granulomatous angiitis of the CNS. In some cases vascular beta-amyloid is also identified and is probably the target of the autoimmune attack [66, 77].

Symptoms of CNS vasculitis may include headache, neurological deficits, and confusion [78]. In contrast to acute stroke, the symptoms are subacute and progressive or waxing and waning, and evolve over days to weeks. Impaired cognition is common. There is minimal information on the pattern of cognitive deficits; a few small case series suggest involvement of attention, processing speed, and visual–spatial functions [79, 80]. Age at onset is usually younger than for typical ischemic stroke, but there is wide variation. Neuroimaging may show edema, small infarcts or hemorrhages, or may be normal. Lumbar puncture may show increased protein and lymphocytic pleocytosis or may be normal. Peripheral markers of inflammation, such as erythrocyte sedimentation rate or C-reactive protein, are usually normal in vasculitis isolated to the CNS but may be elevated when CNS vasculitis complicates a systemic inflammatory disorder. Cerebral angiography shows vascular narrowing when medium-sized arteries are involved, but is usually normal in small vessel vasculitis such as that seen in idiopathic CNS vasculitis. Brain biopsy is needed to make a definitive diagnosis of CNS vasculitis. However, because the disease tends to have a patchy distribution across the brain, even brain biopsy may be falsely negative if an unaffected area was sampled. Brain tissue at the margin of an affected brain region may provide the highest diagnostic yield; however, care should be taken not to biopsy the center of an infarct because it would show only non-diagnostic tissue destruction. There are no proven therapies for CNS vasculitis. Intravenous steroids and immunosuppression are frequently tried, and the disease may go into remission.

Intravascular Large B Cell Lymphoma

Intravascular large B cell lymphoma (also called intravascular lymphomatosis or malignant angioendotheliomatosis) is a rare manifestation of lymphoma caused by occlusion of capillaries and small venules by lymphoma cells. Affected organs include the brain, skin, bone marrow, spleen, and liver. Common neurological manifestations include stroke and progressive cognitive impairment, including rapid-onset dementia [78]. Brain MRI may show small infarcts that enhance after gadolinium contrast injection. Many of the presenting symptoms and signs mimic CNS vasculitis. Biopsy is required to make the diagnosis.

Systemic Lupus Erythematosis

SLE is an autoimmune disease of unknown cause that affects multiple organs including the brain. Non-neurological manifestations include malar rash, arthritis, and anemia. Neuropsychiatric symptoms are relatively common and are part of the diagnostic criteria for the disease [81, 82]. Manifestations of the disease may include stroke, seizures, CNS inflammation, psychosis, and mood disorders. Several different pathophysiologies may lead to CNS complications in lupus, including vasculitis, noninflammatory vasculopathy, hypercoagulability, and autoantibodies reacting against various epitopes including neurons [83].

Stroke may complicate SLE in up to 20 % of persons [84]. Stroke in SLE may be caused by CNS vasculitis, a CNS vasculopathy without frank inflammation, cardioembolism due to nonbacterial valvular vegetations (Libman–Sacks endocarditis), or a hypercoagulable state due to the presence of antiphospholipid antibodies [85].

The neuropsychological syndrome in patients with stroke and SLE will depend on the brain regions affected by the stroke. However, cognitive dysfunction in SLE also occurs independent of stroke. Cognitive deficits may also be identified in the context of concurrent psychiatric illness. Therefore, a combination of both stroke-related and non-stroke-related neuropsychological deficits may be seen. Some degree of cognitive dysfunction may be seen in 20–50 % of stroke-free SLE patients [86–90] and is frequently transitory, with subsequent improvement [88]. Impaired immediate memory and concentration may be seen with acute disease activity, while impaired delayed recognition memory may represent the sequelae of past CNS involvement [91]. Even patients without overt neurological or psychiatric symptoms may exhibit impairments on tests of verbal memory, logical reasoning, visual attention, and working memory [92]. Cognitive outcomes have been proposed as secondary endpoints in trials of disease-modifying therapies [93].

Moyamoya Syndrome

The moyamoya syndrome is marked by gradual tapering occlusion of the terminal carotid artery or proximal middle cerebral artery with associated development of small, fragile arterial collaterals that supply the anterior circulation of the brain [94, 95]. Most commonly the syndrome is idiopathic, but can also occur as a complication of sickle cell disease, autoimmune diseases such as SLE, connective tissue diseases such as neurofibromatosis type I, Down's syndrome, and other diseases. Some cases are familial but the causative genes are unknown. The term *moyamoya* is Japanese and refers to the characteristic appearance of the collateral arteries as a "puff of smoke" on conventional angiography (see Fig. 11.7) [94]. These arteries are often insufficient to maintain cerebral perfusion, leaving the brain in a tenuous, chronically hypoperfused state. Fluctuations in brain perfusion may lead to

Fig. 11.7 Moyamoya disease. Angiography (right internal carotid artery injection, anterior–posterior view) in a 17-year-old woman with familial moyamoya disease shows occlusion of the terminal portion of the right internal carotid artery (*arrow*) with multiple fine collateral vessels (*arrowheads*) supplying blood flow to the right middle cerebral artery
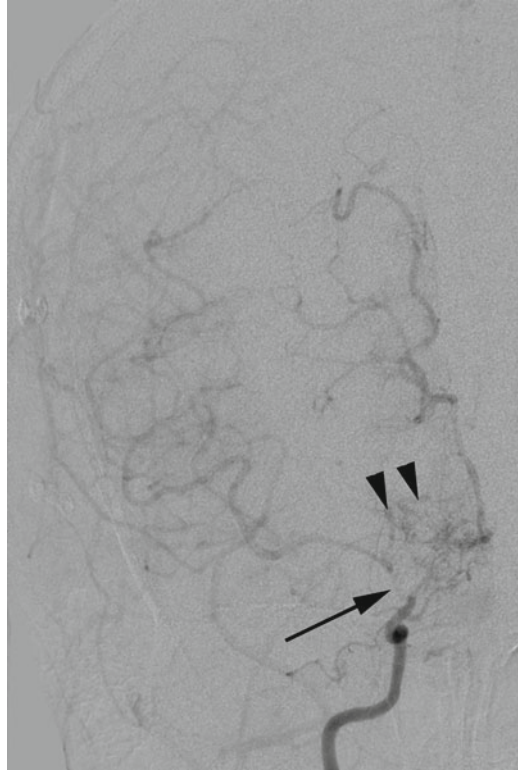
transient ischemia with focal neurological symptoms. Progressive stepwise brain infarction over weeks and months may ensue. Alternatively, the fragile collaterals may rupture and cause ICH.

Moyamoya syndrome usually presents in childhood before the age of 10 years. Transient focal neurological symptoms are the most common presenting symptoms but sometimes cognitive impairment is the dominant symptom [96]. Poor school performance is frequent [97]. Low IQ scores may be seen and may decline over time in some children [98]. Mental retardation with very low IQ is uncommon at presentation, however [99]. More severe global cognitive impairments are usually the result of multiple ischemic strokes. Neuropsychological studies in adults with moyamoya demonstrate impairment in up to a third of patients. Some studies point to impaired executive function as the most prominent finding [100–102], while others have found broader impairments affecting memory as well [103].

Revascularization procedures that restore normal cerebral blood flow may improve IQ in affected children [104, 105]. Long-term outcomes after revascularization are uncertain, with some patients demonstrating stable improvement

but others still suffering from periodic transient ischemic attacks and with borderline low IQ [99, 106]. In some children, IQ worsens over time in the absence of stroke, which may be considered a possible indication for surgical revascularization [107, 108].

Sickle Cell Disease

Sickle cell disease is caused by a mutation in the HBB gene encoding beta-globin, one of the constituents of the hemoglobin molecule. The red blood cells in affected patients can assume a characteristic sickle shape, particularly under conditions of low oxygen, leading to obstruction of capillaries. Patients may have intermittent sickle cell crises, marked by fever, chest pain and diffuse pain, dyspnea, and confusion. Stroke is a common complication and is a leading cause of death [109]. Patients with sickle cell disease are at risk for both ischemic stroke and hemorrhagic stroke. Most strokes are ischemic (67 %) and are caused by occlusion of a large intracranial artery. Progressive stenosis of intracranial arteries may occur, in some cases leading to the moyamoya syndrome. High intracranial arterial blood flow velocities seen on transcranial Doppler ultrasound identify children at higher risk of stroke, and this risk can be reduced by blood transfusions [110]. "Silent" or minimally symptomatic small infarcts can occur in the cerebral white matter and are visible on MRI in 20–30 % of children [111, 112]. Risk factors for ischemic stroke include prior transient ischemic attack, prior episodes of chest pain, lower hemoglobin, and higher blood pressure [113]. Hemorrhagic stroke in sickle cell patients may result from bleeding in the subarachnoid space or the brain and usually occurs in young adults, not children [113]. Sickle cell disease may promote aneurysm formation by causing endothelial dysfunction with secondary changes in the vessel wall. The fragile collateral arteries seen in the moyamoya syndrome can be another source of bleeding.

Cognitive dysfunction in sickle cell disease may be the consequence of symptomatic stroke, or the consequence of "silent" cerebrovascular disease in the absence of symptomatic stroke. Up to one-third of children with sickle cell disease have low IQ [114]. Neuropsychological testing reveals executive dysfunction [114] and lower performance on tests of arithmetic, vocabulary, and visual motor speed and coordination [112]. Neuropsychological test performance is worse in children with silent brain infarcts [112]. However, neuropsychological deficits may also be present in the absence of silent brain infarction, and are correlated with the severity of anemia, microstructural alterations in the cerebral white matter, and lower cerebral blood flow [115–117]. As with children, about one-third of adults have low IQ (more than one standard deviation below the age- and sex-adjusted means) [118]. Executive dysfunction, slower psychomotor processing speed and poor working memory may be seen in adults, even in the absence of symptomatic stroke. Cognitive deficits are worse in patients with more severe anemia [118].

Exchange transfusion lowers the risk of stroke in susceptible patients with sickle cell disease [110]. However, it is not known whether exchange transfusions prevent silent brain infarction or improve cognition. Hydroxyurea is not as effective at preventing strokes as exchange transfusion [119].

Hypercoagulability and Hyperviscosity States

Ischemic stroke caused by hypercoagulability or hyperviscosity is not common. The most frequently encountered cause of hypercoagulability in ischemic stroke is active cancer. Otherwise, ischemic stroke due to hypercoagulability is rare. Autoimmune coagulopathies such as the antiphospholipid antibody syndrome may cause ischemic stroke with secondary vascular dementia [120]. Sneddon's syndrome is caused by antiphospholipid antibodies with thrombosis of small arteries in the skin and brain. Patients present with livedo reticularis, a lacy purple rash usually on the thighs, in conjunction with ischemic stroke. Rarely, patients may present with a progressive dementia caused by multiple "silent" brain infarcts [121, 122]. Thrombotic thrombocytopenic purpura presents with some combination of microangiopathic hemolytic anemia, thrombocytopenia, acute delirium, acute renal failure, and fever [123]. The simultaneous presence of all of these manifestations is uncommon, however, and the diagnosis can be made based on the presence of microangiopathic hemolytic anemia and thrombocytopenia without other apparent cause. Neurological manifestations are caused by small arterial occlusions due to platelet dysfunction. Headache and confusion are common; infarction, coma, and seizures may also occur. A hyperviscosity syndrome may occur due to the very high serum protein levels encountered in Waldenstrom's macroglobulinemia or multiple myeloma [124]. The high blood viscosity impairs cerebral blood flow and can cause symptoms including headache, dizziness, confusion, vision loss, and coma [124].

Cerebral Venous Thrombosis

Thrombosis of cerebral sinuses or veins usually presents subacutely with progressive headache, seizures, or neurological deficits. The cause may be idiopathic, or may be secondary to infection in the mastoid or middle ear, or as a complication of neurosurgery. Risk factors include female sex, oral contraceptive use, factor V Leiden mutation or prothrombin gene mutation, and smoking [125]. Occlusion of cerebral veins or sinuses prevents outflow of blood from the brain that may lead to increased intracranial pressure, edema, and venous infarction. Cognitive symptoms may include decreased arousal and awareness due to globally increased intracranial pressure or focal symptoms due to venous infarction.

Dural Arteriovenous Fistula

Dural arteriovenous fistulas are direct connections between a dural artery and a meningeal vein or dural sinus. Exposure of the venous sinus to arterial pressures can impair brain venous outflow. Rarely, this can lead to an encephalopathy due to venous hypertension that mimics a progressive dementia [126]. In some cases the symptoms may be improved after surgical obliteration of the fistula [127, 128].

Summary

ICH comprises 10–15 % of stroke but is associated with high mortality and morbidity. There are few specific studies of cognitive dysfunction in these patients. Deficits are related to the location and volume of the hemorrhage and will be similar to those occurring in patients with ischemic strokes affecting the same brain regions. In addition, however, patients with non-lobar ICH usually have chronic hypertension that can itself produce neurocognitive deficits. Patients with primary lobar ICH usually have CAA. This may also be associated with preexisting, progressive neurocognitive deficits, and in some cases with Alzheimer's disease. Treatment of cognitive deficits after ICH has seldom been investigated.

References

1. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. Lancet. 2009;373(9675):1632–44. PubMed PMID: 19427958. English.
2. Rosand J, Hylek EM, O'Donnell HC, Greenberg SM. Warfarin-associated hemorrhage and cerebral amyloid angiopathy: a genetic and pathologic study. Neurology. 2000;55(7):947–51. PubMed PMID: 11061249.
3. Smith EE, Rosand J, Greenberg SM. Imaging of hemorrhagic stroke. Magn Reson Imaging Clin N Am. 2006;14(2):127–40. v. PubMed PMID: 16873007.
4. Biffi A, Sonni A, Anderson CD, Kissela B, Jagiella JM, Schmidt H, et al. Variants at APOE influence risk of deep and lobar intracerebral hemorrhage. Ann Neurol. 2010;68(6):934–43. PubMed PMID: 21061402. Epub 2010/11/10. Eng.
5. Woo D, Sauerbeck LR, Kissela BM, Khoury JC, Szaflarski JP, Gebel J, et al. Genetic and environmental risk factors for intracerebral hemorrhage: preliminary results of a population-based study. Stroke. 2002;33(5):1190–5. PubMed PMID: 11988589.
6. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010;376(9735):112–23. PubMed PMID: 20561675. Epub 2010/06/22. eng.
7. Nys GM, van Zandvoort MJ, de Kort PL, Jansen BP, de Haan EH, Kappelle LJ. Cognitive disorders in acute stroke: prevalence and clinical determinants. Cerebrovasc Dis. 2007;23 (5–6):408–16. PubMed PMID: 17406110. Epub 2007/04/05. eng.
8. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol. 2009;8(11):1006–18. PubMed PMID: 19782001. Epub 2009/09/29. eng.

9. Cordonnier C, Leys D, Dumont F, Deramecourt V, Bordet R, Pasquier F, et al. What are the causes of pre-existing dementia in patients with intracerebral haemorrhages? Brain. 2010;133(11):3281–9. PubMed PMID: 20852266. Epub 2010/09/21. eng.

10. Smith EE, Gurol ME, Eng JA, Engel CR, Nguyen TN, Rosand J, et al. White matter lesions, cognition, and recurrent hemorrhage in lobar intracerebral hemorrhage. Neurology. 2004;63(9):1606–12. PubMed PMID: 15534243.

11. Smith EE, Nandigam KR, Chen YW, Jeng J, Salat D, Halpin A, et al. MRI markers of small vessel disease in lobar and deep hemispheric intracerebral hemorrhage. Stroke. 2010;41(9):1933–8. PubMed PMID: 20689084. Epub 2010/08/07. eng.

12. Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. Ann Neurol. 2011;70(6):871–80. PubMed PMID: 22190361. Epub 2011/12/23. eng.

13. Sachdev PS, Chen X, Brodaty H, Thompson C, Altendorf A, Wen W. The determinants and longitudinal course of post-stroke mild cognitive impairment. J Int Neuropsychol Soc. 2009;15(6):915–23. PubMed PMID: 19891821. Epub 2009/11/07. eng.

14. Pendlebury ST, Cuthbertson FC, Welch SJ, Mehta Z, Rothwell PM. Underestimation of cognitive impairment by Mini-Mental State Examination versus the Montreal Cognitive Assessment in patients with transient ischemic attack and stroke: a population-based study. Stroke. 2010;41(6):1290–3. PubMed PMID: 20378863. Epub 2010/04/10. eng.

15. Su CY, Chen HM, Kwan AL, Lin YH, Guo NW. Neuropsychological impairment after hemorrhagic stroke in basal ganglia. Arch Clin Neuropsychol. 2007;22(4):465–74. PubMed PMID: 17336034. English.

16. Su CY, Wuang YP, Chang JK, Guo NW, Kwan AL. Wisconsin Card Sorting Test performance after putaminal hemorrhagic stroke. Kaohsiung J Med Sci. 2006;22(2):75–84. PubMed PMID: 16568724. English.

17. Kawahara N, Sato K, Muraki M, Tanaka K, Kaneko M, Uemura K. CT classification of small thalamic hemorrhages and their clinical implications. Neurology. 1986;36(2):165–72. PubMed PMID: 3945386. Epub 1986/02/01. eng.

18. Mijovic-Prelec D, Bentley P, Caviness Jr VS. Selective rotation of egocentric spatial representation following right putaminal hemorrhage. Neuropsychologia. 2004;42(13):1827–37. PubMed PMID: 15351631. Epub 2004/09/08. eng.

19. Maeshima S, Truman G, Smith DS, Dohi N, Nakai K, Itakura T, et al. Apraxia and cerebral haemorrhage: the relationship between haematoma volume and prognosis. J Clin Neurosci. 2000;7(4):309–11. PubMed PMID: 10938607. Epub 2000/08/12. eng.

20. Kawanishi M, Kajikawa H, Yamamura K, Nomura E, Kajikawa M, Hihara R, et al. Aphasia following left putaminal hemorrhage. Statistical analysis of factors affecting prognosis. Neurol Res. 2002;24(8):817–21. PubMed PMID: 12500706. Epub 2002/12/26. eng.

21. Damasio H, Damasio AR. The anatomical basis of conduction aphasia. Brain. 1980;103(2):337–50. PubMed PMID: 7397481. Epub 1980/06/01. eng.

22. Naeser MA, Hayward RW. The resolving stroke and aphasia. A case study with computerized tomography. Arch Neurol. 1979;36(4):233–5. PubMed PMID: 426669. Epub 1979/04/01. eng.

23. Maeshima S, Truman G, Smith DS, Dohi N, Itakura T, Komai N. Buccofacial apraxia and left cerebral haemorrhage. Brain Inj. 1997;11(11):777–82. PubMed PMID: 9354254. Epub 1997/11/14. eng.

24. Fuh JL, Wang SJ. Caudate hemorrhage: clinical features, neuropsychological assessments and radiological findings. Clin Neurol Neurosurg. 1995;97(4):296–9. PubMed PMID: 8599895. Epub 1995/11/01. eng.

25. Su CY, Chang JJ, Chen HM, Su CJ, Chien TH, Huang MH. Perceptual differences between stroke patients with cerebral infarction and intracerebral hemorrhage. Arch Phys Med Rehabil. 2000;81(6):706–14. PubMed PMID: 10857510. Epub 2000/06/17. eng.

26. Bhatia KP, Marsden CD. The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain. 1994;117(Pt 4):859–76. PubMed PMID: 7922471. Epub 1994/08/01. eng.

27. Maeshima S, Ueyoshi A, Matsumoto T, Boh-oka S, Yoshida M, Itakura T, et al. Unilateral spatial neglect in patients with cerebral hemorrhage: the relationship between hematoma volume and prognosis. J Clin Neurosci. 2002;9(5):544–8. PubMed PMID: 12383412. Epub 2002/10/18. eng.

28. Morgenstern LB, Hemphill III JC, Anderson C, Becker K, Broderick JP, Connolly Jr ES, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2010;41(9):2108–29. PubMed PMID: 20651276. Epub 2010/07/24. eng.

29. Hemphill III JC, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001;32(4):891–7. PubMed PMID: 11283388.

30. Rost NS, Smith EE, Chang Y, Snider RW, Chanderraj R, Schwab K, et al. Prediction of functional outcome in patients with primary intracerebral hemorrhage: the FUNC score. Stroke. 2008;39(8):2304–9. PubMed PMID: 18556582.

31. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. Lancet. 2005;365(9457):387–97. PubMed PMID: 15680453.

32. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurol. 2008;7(5):391–9. PubMed PMID: 18396107.

33. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med. 2008;358(20):2127–37. PubMed PMID: 18480205.

34. O'Donnell HC, Rosand J, Knudsen KA, Furie KL, Segal AZ, Chiu RI, et al. Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. N Engl J Med. 2000;342(4):240–5. PubMed PMID: 10648765.

35. Biffi A, Halpin A, Towfighi A, Gilson A, Busl K, Rost NS, et al. Antiplatelet agents and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. Neurology. 2010;75(8):693–8.

36. Chapman N, Huxley R, Anderson C, Bousser MG, Chalmers J, Colman S, et al. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. Stroke. 2004;35(1):116–21. PubMed PMID: 14671247.

37. Arima H, Tzourio C, Anderson C, Woodward M, Bousser MG, MacMahon S, et al. Effects of perindopril-based lowering of blood pressure on intracerebral hemorrhage related to amyloid angiopathy: the PROGRESS trial. Stroke. 2010;41(2):394–6. PubMed PMID: 20044530. Epub 2010/01/02. eng.

38. Fazekas F, Kleinert R, Roob G, Kleinert G, Kapeller P, Schmidt R, et al. Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. AJNR Am J Neuroradiol. 1999;20(4):637–42.

39. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Salman RA, Warach S, et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol. 2009;8(2):165–74. PubMed PMID: 19161908. English.

40. Jeerakathil T, Wolf PA, Beiser A, Hald JK, Au R, Kase CS, et al. Cerebral microbleeds: prevalence and associations with cardiovascular risk factors in the Framingham Study. Stroke. 2004;35(8):1831–5. PubMed PMID: 15155954.

41. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. Neurology. 2001;56(4):537–9. PubMed PMID: 11222803.

42. Werring DJ, Frazer DW, Coward LJ, Losseff NA, Watt H, Cipolotti L, et al. Cognitive dysfunction in patients with cerebral microbleeds on T2*-weighted gradient-echo MRI. Brain. 2004;127(Pt 10):2265–75. PubMed PMID: 15282216.

43. Cordonnier C, Potter GM, Jackson CA, Doubal F, Keir S, Sudlow CL, et al. Improving interrater agreement about brain microbleeds: development of the Brain Observer MicroBleed Scale (BOMBS). Stroke. 2009;40(1):94–9. PubMed PMID: 19008468.

44. Pettersen JA, Sathiyamoorthy G, Gao FQ, Szilagyi G, Nadkarni NK, St George-Hyslop P, et al. Microbleed topography, leukoaraiosis, and cognition in probable Alzheimer disease from the Sunnybrook dementia study. Arch Neurol. 2008;65(6):790–5. PubMed PMID: 18541799. English.

45. Atri A, Locascio JJ, Lin JM, Yap L, Dickerson BC, Grodstein F, et al. Prevalence and effects of lobar microhemorrhages in early-stage dementia. Neurodegener Dis. 2005;2(6):305–12. PubMed PMID: 16909013. English.

46. Goos JD, Kester MI, Barkhof F, Klein M, Blankenstein MA, Scheltens P, et al. Patients with Alzheimer disease with multiple microbleeds: relation with cerebrospinal fluid biomarkers and cognition. Stroke. 2009;40(11):3455–60. PubMed PMID: 19762705. Epub 2009/09/19. eng.

47. Henneman WJ, Sluimer JD, Cordonnier C, Baak MM, Scheltens P, Barkhof F, et al. MRI biomarkers of vascular damage and atrophy predicting mortality in a memory clinic population. Stroke. 2009;40(2):492–8. PubMed PMID: 19109551. Epub 2008/12/26. eng.

48. Kirsch W, McAuley G, Holshouser B, Petersen F, Ayaz M, Vinters HV, et al. Serial susceptibility weighted MRI measures brain iron and microbleeds in dementia. J Alzheimers Dis. 2009;17(3):599–609. PubMed PMID: 19433895. Pubmed Central PMCID: 2788087. Epub 2009/05/13. eng.

49. Staekenborg SS, Koedam EL, Henneman WJ, Stokman P, Barkhof F, Scheltens P, et al. Progression of mild cognitive impairment to dementia: contribution of cerebrovascular disease compared with medial temporal lobe atrophy. Stroke. 2009;40(4):1269–74. PubMed PMID: 19228848. Epub 2009/02/21. eng.

50. Seo SW, Hwa Lee B, Kim EJ, Chin J, Sun Cho Y, Yoon U, et al. Clinical significance of microbleeds in subcortical vascular dementia.[see comment]. Stroke. 2007;38(6):1949–51. PubMed PMID: 17510457. English.

51. Yakushiji Y, Nishiyama M, Yakushiji S, Hirotsu T, Uchino A, Nakajima J, et al. Brain microbleeds and global cognitive function in adults without neurological disorder. Stroke. 2008;39(12):3323–8. PubMed PMID: 18688000. English.

52. Van Es AC, van der Grond J, de Craen AJ, Westendorp RG, Bollen EL, Blauw GJ, et al. Cerebral microbleeds and cognitive functioning in the PROSPER study. Neurology. 2011;77(15):1446–52.

53. Takashima Y, Mori T, Hashimoto M, Kinukawa N, Uchino A, Yuzuriha T, et al. Clinical correlating factors and cognitive function in community-dwelling healthy subjects with cerebral microbleeds. J Stroke Cerebrovasc Dis. 2011;20(2):105–10.

54. Vinters HV. Cerebral amyloid angiopathy. A critical review. Stroke. 1987;18(2):311–24.

55. Revesz T, Holton JL, Lashley T, Plant G, Frangione B, Rostagno A, et al. Genetics and molecular pathogenesis of sporadic and hereditary cerebral amyloid angiopathies. Acta Neuropathol. 2009;118(1):115–30. PubMed PMID: 19225789. Epub 2009/02/20. eng.

56. Vonsattel JP, Myers RH, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson Jr EP. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. Ann Neurol. 1991;30(5):637–49. PubMed PMID: 1763890.

57. Keage HA, Carare RO, Friedland RP, Ince PG, Love S, Nicoll JA, et al. Population studies of sporadic cerebral amyloid angiopathy and dementia: a systematic review. BMC Neurol. 2009;9(1):3. PubMed PMID: 19144113.

58. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales Lancet. 2001;357(9251):169–175. PubMed PMID: 11213093.

59. Smith EE, Greenberg SM. Beta-amyloid, blood vessels, and brain function. Stroke. 2009;40(7):2601–6. PubMed PMID: 19443808. Pubmed Central PMCID: 2704252. Epub 2009/05/16. eng.

60. Weller RO, Boche D, Nicoll JA. Microvasculature changes and cerebral amyloid angiopathy in Alzheimer's disease and their potential impact on therapy. Acta Neuropathol. 2009;118(1):87–102. PubMed PMID: 19234858. English.

61. Greenberg SM, Rebeck GW, Vonsattel JP, Gomez-Isla T, Hyman BT. Apolipoprotein E epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. Ann Neurol. 1995;38(2):254–9.

62. Greenberg SM, Vonsattel JP, Segal AZ, Chiu RI, Clatworthy AE, Liao A, et al. Association of apolipoprotein E epsilon2 and vasculopathy in cerebral amyloid angiopathy. Neurology. 1998;50(4):961–5.

63. Rosand J, Muzikansky A, Kumar A, Wisco JJ, Smith EE, Betensky RA, et al. Spatial clustering of hemorrhages in probable cerebral amyloid angiopathy. Ann Neurol. 2005;58(3):459–62. PubMed PMID: 16130107.

64. Johnson KA, Gregas M, Becker JA, Kinnecom C, Salat DH, Moran EK, et al. Imaging of amyloid burden and distribution in cerebral amyloid angiopathy. Ann Neurol. 2007;62:229–34.

65. Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. Neurology. 2010;74(17):1346–50.

66. Kinnecom C, Lev MH, Wendell L, Smith EE, Rosand J, Frosch MP, et al. Course of cerebral amyloid angiopathy-related inflammation. Neurology. 2007;68(17):1411–6. PubMed PMID: 17452586.

67. Matthews FE, Brayne C, Lowe J, McKeith I, Wharton SB, Ince P. Epidemiological pathology of dementia: attributable-risks at death in the Medical Research Council Cognitive Function and Ageing Study. PLoS Med. 2009;6(11):e1000180. PubMed PMID: 19901977. Epub 2009/11/11. eng.

68. Pfeifer LA, White LR, Ross GW, Petrovitch H, Launer LJ. Cerebral amyloid angiopathy and cognitive function: the HAAS autopsy study. Neurology. 2002;58(11):1629–34.

69. Arvanitakis Z, Leurgans SE, Wang Z, Wilson RS, Bennett DA, Schneider JA. Cerebral amyloid angiopathy pathology and cognitive domains in older persons. Ann Neurol. 2011;69(2):320–7. PubMed PMID: 21387377. Epub 2011/03/10. eng.

70. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG. Cadasil. Lancet Neurol. 2009;8(7):643–53. PubMed PMID: 19539236. Epub 2009/06/23. eng.

71. Dichgans M, Mayer M, Uttner I, Bruning R, Muller-Hocker J, Rungger G, et al. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. Ann Neurol. 1998;44(5):731–9.

72. Charlton RA, Morris RG, Nitkunan A, Markus HS. The cognitive profiles of CADASIL and sporadic small vessel disease. Neurology. 2006;66(10):1523–6. PubMed PMID: 16717212. English.

73. Dichgans M. Cognition in CADASIL. Stroke. 2009;40(3 Suppl):S45–7. PubMed PMID: 19064778. English.

74. Reyes S, Viswanathan A, Godin O, Dufouil C, Benisty S, Hernandez K, et al. Apathy: a major symptom in CADASIL. Neurology. 2009;72(10):905–10. PubMed PMID: 19273824. Epub 2009/03/11. eng.

75. Dichgans M, Markus HS, Salloway S, Verkkoniemi A, Moline M, Wang Q, et al. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. Lancet Neurol. 2008;7(4):310–8. PubMed PMID: 18296124.

76. Hajj-Ali RA, Singhal AB, Benseler S, Molloy E, Calabrese LH. Primary angiitis of the CNS. Lancet Neurol. 2011;10(6):561–72. PubMed PMID: 21601163. Epub 2011/05/24. eng.

77. Scolding NJ, Joseph F, Kirby PA, Mazanti I, Gray F, Mikol J, et al. Abeta-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. Brain. 2005;128(Pt 3):500–15. PubMed PMID: 15659428.

78. Glass J, Hochberg F, Miller DC. Intravascular lymphomatosis: a systemic disease with neurologic manifestations. Cancer. 2006;71(10):3145–64.

79. Casato M, Saadoun D, Marchetti A, Limal N, Picq C, Pantano P, et al. Central nervous system involvement in hepatitis C virus cryoglobulinemia vasculitis: a multicenter case-control study using magnetic resonance imaging and neuropsychological tests. J Rheumatol. 2005;32(3):484–8.

80. Mattioli F, Capra R, Rovaris M, Chiari S, Codella M, Miozzo A, et al. Frequency and patterns of subclinical cognitive impairment in patients with ANCA-associated small vessel vasculitides. J Neurol Sci. 2002;195(2):161–6.

81. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725. PubMed PMID: 9324032. Epub 1997/10/27. eng.

82. American College of Rheumatology Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 1999;42(4):599–608. PubMed PMID: 10211873.

83. Colasanti T, Delunardo F, Margutti P, Vacirca D, Piro E, Siracusano A, et al. Autoantibodies involved in neuropsychiatric manifestations associated with systemic lupus erythematosus. J Neuroimmunol. 2009;212(1–2):3–9. PubMed PMID: 19500858. Epub 2009/06/09. eng.

84. Mikdashi J, Handwerger B, Langenberg P, Miller M, Kittner S. Baseline disease activity, hyperlipidemia, and hypertension are predictive factors for ischemic stroke and stroke severity in systemic lupus erythematosus. Stroke. 2007;38(2):281–5. PubMed PMID: 17218611. Epub 2007/01/16. eng.

85. Futrell N, Millikan C. Frequency, etiology, and prevention of stroke in patients with systemic lupus erythematosus. Stroke. 1989;20(5):583–91. PubMed PMID: 2718197. Epub 1989/05/01. eng.

86. Monastero R, Bettini P, Del Zotto E, Cottini E, Tincani A, Balestrieri G, et al. Prevalence and pattern of cognitive impairment in systemic lupus erythematosus patients with and without overt neuropsychiatric manifestations. J Neurol Sci. 2001;184(1):33–9. PubMed PMID: 11231030. Epub 2001/03/07. eng.

87. Loukkola J, Laine M, Ainiala H, Peltola J, Metsanoja R, Auvinen A, et al. Cognitive impairment in systemic lupus erythematosus and neuropsychiatric systemic lupus erythematosus: a population-based neuropsychological study. J Clin Exp Neuropsychol. 2003;25(1):145–51. PubMed PMID: 12607179. Epub 2003/02/28. eng.

88. Hanly JG, Fisk JD, Sherwood G, Eastwood B. Clinical course of cognitive dysfunction in systemic lupus erythematosus. J Rheumatol. 1994;21(10):1825–31. PubMed PMID: 7837145. Epub 1994/10/01. eng.

89. Denburg SD, Denburg JA, Carbotte RM, Fisk JD, Hanly JG. Cognitive deficits in systemic lupus erythematosus. Rheum Dis Clin North Am. 1993;19(4):815–31. PubMed PMID: 8265824. Epub 1993/11/01. eng.

90. Nowicka-Sauer K, Czuszynska Z, Smolenska Z, Siebert J. Neuropsychological assessment in systemic lupus erythematosus patients: clinical usefulness of first-choice diagnostic tests in detecting cognitive impairment and preliminary diagnosis of neuropsychiatric lupus. Clin Exp Rheumatol. 2011;29(2):299–306. PubMed PMID: 21418780. Epub 2011/03/23. eng.

91. Fisk JD, Eastwood B, Sherwood G, Hanly JG. Patterns of cognitive impairment in patients with systemic lupus erythematosus. Br J Rheumatol. 1993;32(6):458–62. PubMed PMID: 8508281. Epub 1993/06/01. eng.

92. Kozora E, Arciniegas DB, Filley CM, West SG, Brown M, Miller D, et al. Cognitive and neurologic status in patients with systemic lupus erythematosus without major neuropsychiatric syndromes. Arthritis Rheum. 2008;59(11):1639–46. PubMed PMID: 18975359. Epub 2008/11/01. eng.

93. Mikdashi JA, Esdaile JM, Alarcon GS, Crofford L, Fessler BJ, Shanberg L, et al. Proposed response criteria for neurocognitive impairment in systemic lupus erythematosus clinical trials. Lupus. 2007;16(6):418–25. PubMed PMID: 17664232. Epub 2007/08/01. eng.

94. Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. Arch Neurol. 1969;20(3):288–99. PubMed PMID: 5775283.

95. Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. N Engl J Med. 2009;360(12):1226–37. PubMed PMID: 19297575. English.

96. Levin SD, Hoare RD, Robinson RO. Childhood moyamoya presenting as dementia: report of a case. Dev Med Child Neurol. 1983;25(6):794–7. PubMed PMID: 6653912.

97. Sato H, Sato N, Tamaki N, Matsumoto S. Chronic low-perfusion state in children with moy-amoya disease following revascularization. Childs Nerv Syst. 1990;6(3):166–71. PubMed PMID: 2357714.

98. Hogan AM, Kirkham FJ, Isaacs EB, Wade AM, Vargha-Khadem F. Intellectual decline in children with moyamoya and sickle cell anaemia. Dev Med Child Neurol. 2005;47(12):824–9. PubMed PMID: 16288673. Epub 2005/11/18. eng.

99. Karasawa J, Touho H, Ohnishi H, Miyamoto S, Kikuchi H. Long-term follow-up study after extracranial-intracranial bypass surgery for anterior circulation ischemia in childhood moy-amoya disease. J Neurosurg. 1992;77(1):84–9. PubMed PMID: 1607976.

100. Weinberg DG, Rahme RJ, Aoun SG, Batjer HH, Bendok BR. Moyamoya disease: functional and neurocognitive outcomes in the pediatric and adult populations. Neurosurg Focus. 2011;30(6):E21. PubMed PMID: 21631223. Epub 2011/06/03. eng.

101. Calviere L, Catalaa I, Marlats F, Viguier A, Bonneville F, Cognard C, et al. Correlation between cognitive impairment and cerebral hemodynamic disturbances on perfusion mag-netic resonance imaging in European adults with moyamoya disease. Clinical article. J Neurosurg. 2010;113(4):753–9. PubMed PMID: 20469988. Epub 2010/05/18. eng.

102. Karzmark P, Zeifert PD, Tan S, Dorfman LJ, Bell-Stephens TE, Steinberg GK. Effect of moyamoya disease on neuropsychological functioning in adults. Neurosurgery. 2008;62(5):1048–51; discussion 51–2. PubMed PMID: 18580802. Epub 2008/06/27. eng.

103. Festa JR, Schwarz LR, Pliskin N, Cullum CM, Lacritz L, Charbel FT, et al. Neurocognitive dysfunction in adult moyamoya disease. J Neurol. 2010;257(5):806–15. PubMed PMID: 20033200. Epub 2009/12/25. eng.

104. Ishii R, Takeuchi S, Ibayashi K, Tanaka R. Intelligence in children with moyamoya disease: evaluation after surgical treatments with special reference to changes in cerebral blood flow. Stroke. 1984;15(5):873–7. PubMed PMID: 6474539.

105. Lee JY, Phi JH, Wang KC, Cho BK, Shin MS, Kim SK. Neurocognitive profiles of children with moyamoya disease before and after surgical intervention. Cerebrovasc Dis. 2011;31(3):230–7. PubMed PMID: 21178347. Epub 2010/12/24. eng.

106. Matsushima Y, Aoyagi M, Nariai T, Takada Y, Hirakawa K. Long-term intelligence outcome of post-encephalo-duro-arterio-synangiosis childhood moyamoya patients. Clin Neurol Neurosurg. 1997;99 Suppl 2:S147–50. PubMed PMID: 9409426.

107. Imaizumi C, Imaizumi T, Osawa M, Fukuyama Y, Takeshita M. Serial intelligence test scores in pediatric moyamoya disease. Neuropediatrics. 1999;30(6):294–9. PubMed PMID: 10706023.

108. Matsushima Y, Aoyagi M, Niimi Y, Masaoka H, Ohno K. Symptoms and their pattern of progression in childhood moyamoya disease. Brain Dev. 1990;12(6):784–9. PubMed PMID: 2092589.

109. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639–44. PubMed PMID: 7993409. Epub 1994/06/09. eng.

110. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998;339(1):5–11. PubMed PMID: 9647873.

111. Debaun MR, Sarnaik SA, Rodeghier MJ, Minniti CP, Howard TH, Iyer RV, et al. Associated risk factors for silent cerebral infarcts in sickle cell anemia: low baseline hemoglobin, gender and relative high systolic blood pressure. Blood. 2011;119(16):3684–90. PubMed PMID: 22096242. Epub 2011/11/19. Eng.

112. Armstrong FD, Thompson Jr RJ, Wang W, Zimmerman R, Pegelow CH, Miller S, et al. Cognitive functioning and brain magnetic resonance imaging in children with sickle cell disease. Neuropsychology Committee of the Cooperative Study of Sickle Cell Disease. Pediatrics. 1996;97(6 Pt 1):864–70. PubMed PMID: 8657528. Epub 1996/06/01. eng.

113. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998;91(1):288–94. PubMed PMID: 9414296. Epub 1998/02/07. eng.

114. Hijmans CT, Fijnvandraat K, Grootenhuis MA, van Geloven N, Heijboer H, Peters M, et al. Neurocognitive deficits in children with sickle cell disease: a comprehensive profile. Pediatr Blood Cancer. 2011;56(5):783–8. PubMed PMID: 21370411. Epub 2011/03/04. eng.

115. Scantlebury N, Mabbott D, Janzen L, Rockel C, Widjaja E, Jones G, et al. White matter integrity and core cognitive function in children diagnosed with sickle cell disease. J Pediatr Hematol Oncol. 2011;33(3):163–71. PubMed PMID: 21325970. Epub 2011/02/18. eng.

116. Hijmans CT, Grootenhuis MA, Oosterlaan J, Heijboer H, Peters M, Fijnvandraat K. Neurocognitive deficits in children with sickle cell disease are associated with the severity of anemia. Pediatr Blood Cancer. 2011;57(2):297–302. PubMed PMID: 21671366. Epub 2011/06/15. eng.

117. Strouse JJ, Cox CS, Melhem ER, Lu H, Kraut MA, Razumovsky A, et al. Inverse correlation between cerebral blood flow measured by continuous arterial spin-labeling (CASL) MRI and neurocognitive function in children with sickle cell anemia (SCA). Blood. 2006;108(1):379–81. PubMed PMID: 16537809. Pubmed Central PMCID: 1482738. Epub 2006/03/16. eng.

118. Vichinsky EP, Neumayr LD, Gold JI, Weiner MW, Rule RR, Truran D, et al. Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. JAMA. 2010;303(18):1823–31. PubMed PMID: 20460621. Pubmed Central PMCID: 2892214. Epub 2010/05/13. eng.

119. Ware RE, Helms RW. Stroke with transfusions changing to hydroxyurea (SWiTCH). Blood. 2012;119(17):3925–32. PubMed PMID: 22318199. Epub 2012/02/10. Eng.

120. Gomez-Puerta JA, Cervera R, Calvo LM, Gomez-Anson B, Espinosa G, Claver G, et al. Dementia associated with the antiphospholipid syndrome: clinical and radiological characteristics of 30 patients. Rheumatology (Oxford). 2005;44(1):95–9. PubMed PMID: 15367749. Epub 2004/09/16. eng.

121. Wright RA, Kokmen E. Gradually progressive dementia without discrete cerebrovascular events in a patient with Sneddon's syndrome. Mayo Clin Proc. 1999;74(1):57–61. PubMed PMID: 9987534. Epub 1999/02/13. eng.

122. Wilson WB, Smith DB, Wright RR, Seibert CE. Sneddon's disease presenting with visual loss and dementia. J Clin Neuroophthalmol. 1988;8(4):255–61. PubMed PMID: 2977141. Epub 1988/12/01. eng.

123. George JN. Clinical practice. Thrombotic thrombocytopenic purpura. N Engl J Med. 2006;354(18):1927–35. PubMed PMID: 16672704. Epub 2006/05/05. eng.

124. Mehta J, Singhal S. Hyperviscosity syndrome in plasma cell dyscrasias. Semin Thromb Hemost. 2003;29(5):467–71. PubMed PMID: 14631546. Epub 2003/11/25. eng.

125. Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol. 2007;6(2):162–70. PubMed PMID: 17239803. Epub 2007/01/24. eng.

126. Hurst RW, Bagley LJ, Galetta S, Glosser G, Lieberman AP, Trojanowski J, et al. Dementia resulting from dural arteriovenous fistulas: the pathologic findings of venous hypertensive encephalopathy. AJNR Am J Neuroradiol. 1998;19(7):1267–73. PubMed PMID: 9726465. Epub 1998/09/03. eng.

127. Datta NN, Rehman SU, Kwok JC, Chan KY, Poon CY. Reversible dementia due to dural arteriovenous fistula: a simple surgical option. Neurosurg Rev. 1998;21(2–3):174–6. PubMed PMID: 9795956. Epub 1998/10/31. eng.

128. Zeidman SM, Monsein LH, Arosarena O, Aletich V, Biafore JA, Dawson RC, et al. Reversibility of white matter changes and dementia after treatment of dural fistulas. AJNR Am J Neuroradiol. 1995;16(5):1080–3. PubMed PMID: 7543726. Epub 1995/05/01. eng.