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The importance of specific diagnosis in stroke patient management

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Introduction: A stroke is not a 'stroke'

Stroke cannot be considered a diagnosis in itself. Stroke refers to any damage to the brain or spinal cord caused by a vascular abnormality, the term generally being reserved for when symptoms begin abruptly. Stroke is anything but a homogeneous entity, encompassing disorders as different as rupture of a large blood vessel that causes flooding of the subarachnoid space with blood, the occlusion of a tiny artery supplying a small but strategic brain site and thrombosis of a venous conduit obstructing outflow of blood from the brain. Each stroke subtype carries with it different implications for acute treatment, prognosis and secondary prevention. Each stroke patient has additional variables that influence management, including the time from onset to presentation, the severity of the lesion, and associated comorbidities as well as social and psychological factors. The availability of non-invasive imaging techniques has revolutionized the diagnostic process, enabling a much greater understanding of the relevant pathophysiological processes active in the individual patient. This chapter provides an overview of how the specific diagnostic information available from non-invasive investigations can be applied to the management of individual patients.

'Lumping' vs. 'splitting'

The goal of every clinician is to provide the best care for his or her patients. Where possible, physicians should manage patients according to methods that have been tested by well-designed randomized controlled trials. Unfortunately, few therapies for patients with stroke have been tested with randomized trials, and even fewer have been thoroughly investigated for patients with specific stroke subtypes.

Randomized trials have limitations, including the issue of numbers v. specificity, or 'lumping' v. 'splitting'. To provide statistically valid results, randomized trials must contain large numbers of patients with enough end points to analyse within a relatively short period; therefore 'lumping' must predominate over 'splitting'. But, if the results are to be useful for clinical practice, the data must be specifically applicable to individual patients. Too often, there are significant obstacles to doing this. Investigators have continued to design trials as if they expect a single treatment to be effective for all ischemic stroke patients, resulting in inevitable disappointment. Even when treatments have been found effective, there is still a great deal of room for improvement. For example, aspirin has been proven to be effective for early secondary prevention of 'stroke' generally, but only prevents 25% of recurrent strokes within 14 days.[1,2] Cost containment and the need to involve a large number of centres with varying expertise and resources in trials results in a minimum of patient investigation. As a result, accurate subgroup comparisons in trials become impossible, even when these are reported in a *post hoc* analysis. Patients who are too ill, old, young, or of child-bearing age are often excluded

from trials. Those unable to give informed consent or who have too complex, or multiple, illnesses are also frequently left out. The type of patients that are excluded from these trials are those that doctors are called on to care for every day.

The term 'evidence-based' must be used cautiously when applied to a particular circumstance if that circumstance has not been specifically studied. Information from trials must be weighed according to the context of specific treatment decisions for individual patients. George Thibault said it well:[3]

> We then need to decide which approach in our large therapeutic armamentarium will be most appropriate in a particular patient, with a particular stage of diseases and particular coexisting conditions, and at a particular age. Even when randomized clinical trials have been performed (which is true for only a small minority of clinical problems), they will often not answer this question specifically for the patient sitting in front of us in the office or lying in the hospital bed.

The complexity of managing stroke patients is increasing. Improvements in diagnostic accuracy have raised new questions about the correct application of existing treatments. There have been many new developments in stroke therapeutics, including intravenous and intra-arterial thrombolysis, catheter-based interventions such as angioplasty and stenting for both extracranial and intracranial stenoses, the development of new antiplatelet agents with potentially complimentary mechanisms of action, and hypothermic treatment, to name a few. The exact place for all of these therapies is not established, yet it is extremely likely that many of the new treatments that are currently 'unproven' will be able to deliver improved outcomes for carefully selected patients. Ignoring these new diagnostic and therapeutic developments is not an option, although a conservative approach must be taken when potentially hazardous therapies have not been rigorously tested. A specific diagnosis is required to optimize treatment selection.

Advances in imaging and stroke diagnosis

Advances in imaging have led to dramatic changes in our understanding of stroke pathophysiology and how we diagnose stroke. Early stroke classifications relied on clinical information. Terms such as 'transient ischemic attack (TIA)', 'minor stroke', 'reversible ischemic neurologic deficit (RIND)', 'stroke in progress' and 'completed stroke' were used to distinguish stroke subtypes.[4] These simplistic distinctions now have little clinical usefulness. Even the term 'TIA' is becoming obsolete as smaller infarctions have become detectable with magnetic resonance imaging (MRI).[5]

Subsequent classifications have increasingly focused on stroke etiology, because of its importance in determining treatment strategies for secondary prevention of stroke (Table 1.1). This has required an increasing emphasis on the results of imaging investigations, rather than clinical features. The authors of the Trial of Org 10172 in Acute

Table 1.1. Stroke classification

(a)	Clinical stroke classification systems
	'Traditional'
	Transient ischemic attack (TIA)
	Minor stroke
	Reversible ischemic neurologic deficit (RIND)
	Stroke in progress
	Completed stroke
	Oxfordshire Community Stroke Project[6]
	Total anterior cerebral infarction syndrome (TACI)
	Partial anterior cerebral infarction syndrome (PACI)
	Lacunar infarction syndrome (LACI)
	Posterior cerebral infarction syndrome (POCI)
(b)	Etiologic classification systems
	TOAST[7]
	Large artery
	Cardioembolism
	Small vessel
	Other determined etiology
	Undetermined etiology
	Baltimore-Washington[8]
	Atherosclerotic vasculopathy
	Non-atherosclerotic vasculopathy
	Vasculopathy of uncertain cause (lacunar infarct)
	Cardiac/transcardiac embolism
	Hematological/other
	Migrainous stroke
	Oral contraceptive or exogenous estrogen use
	Other drug related
	Indeterminate

Stroke Treatment (TOAST) classified strokes as being due to large artery atherosclerosis, cardioembolism, small vessel occlusion, other determined etiology or undetermined etiology.[7] This system of stroke classification represents an important advance, but still has shortcomings that limit its application to the diagnosis and management of individual patients. One major limitation is the oversimplified 'large artery' classification. This category 'lumps' embolic strokes from sources in the aorta, large vessel origins in the thorax, cervical arterial lesions, and intracranial arterial stenoses with strokes due to thrombotic occlusion of cervical or intracranial vessels of either anterior or posterior circulations.

Stroke subtype classifications used today, such as the TOAST system, reflect the type of stroke imaging techniques that were generally available a decade ago, namely non-contrast computed tomography (CT) head scan and ultrasound examinations of the cervical carotid arteries and of the heart. A diagnostic strategy that continues to rely solely on these modalities will not achieve a more accurate diagnosis. Not only are important parts of the vascular system overlooked entirely by such an approach, but the accuracy of even these simple classifications is often poor.[9] A lacunar stroke cannot be reliably diagnosed on the basis of clinical and acute CT findings.[10] Some patients with a lacunar syndrome have multiple acute lesions on diffusion-weighted MRI, consistent with an embolic etiology.[11] Moreover, diagnosis using the traditional approach is not made in real time, but retrospectively. A subacute CT scan is required if the diagnosis of lacunar infarction is to be confirmed and a cortical lesion excluded. Ultrasound tests may be obtained days after the initial presentation. This is a critical limitation that prevents a specific diagnosis prior to consideration of acute stroke therapies that can only be overcome if other protocols for acute imaging and assessment are used.[9]

Newer imaging techniques that allow rapid, non-invasive assessment of a much greater extent of the vascular system are now widely available. MRI, as this book demonstrates, is an extremely powerful technique for imaging the brain and cerebrovascular system. Brain MRI examinations for stroke should routinely include magnetic resonance angiography (MRA) of the intracranial vasculature. Magnetic resonance venography (MRV) and MRA of the cervical carotid and vertebral arteries can easily be performed at the same sitting as brain imaging, without the need for contrast. Assessment of the aortic arch and proximal vessels is possible with gadolinium-enhanced MRA. Diffusion-weighted MR imaging (DWI) and perfusion imaging (PI) enable determination in real time of the presence and severity of an ischemic deficit and the response of the brain to the insult. These new techniques enable the concept of stroke diagnosis to go beyond that of simple stroke etiology to establish a comprehensive and dynamic model of stroke pathophysiology for individual patients.

Initial stroke diagnosis

Stroke or stroke-mimic

The initial diagnostic step should be to determine if the event is due to stroke or a non-vascular stroke mimic. Clinical information remains very important in distinguishing disorders such as migraine, seizure, and factitious and psychogenic disorders from stroke. Sometimes the diagnosis is relatively clear, but when this is not the case, imaging results are critical. A typical appearance on a CT scan will often confirm the diagnosis of stroke; however, false-negative CT findings are common in the acute phase, particularly if image quality is poor, readers are inexperienced or if the patient presents with lacunar or brainstem stroke.[10,12–14] Diffusion-weighted MRI is extremely sensitive to acute brain ischemia and false-negatives are very rare, with the exception of small brainstem lacunes.[12,15] DWI is therefore the diagnostic modality of choice when the diagnosis of stroke is uncertain and positive evidence of a stroke is required. The importance of an accurate diagnosis even at this level should not be underestimated; as many as 20% of initial stroke diagnoses are erroneous,[16] and some patients with stroke mimic have been treated with thrombolysis as a result.[17]

Arterial occlusion, arterial rupture, or venous thrombosis

The next level of stroke diagnosis is primarily to distinguish hemorrhagic from ischemic stroke. However, conceptualizing the mechanism and its vascular pathology ensures that stroke due to venous thrombosis is not overlooked. The majority of the remainder of the chapter considers diagnosis of ischemic stroke; cerebral venous thrombosis and hemorrhagic stroke are considered briefly below.

Cerebral venous thrombosis

Although cerebral venous thrombosis (CVT) is rare in comparison with other stroke types, it is treatable and the diagnosis is frequently missed on CT scan. MRI is very sensitive in the detection of CVT;[18] however, the diagnosis can be overlooked if it is not considered in the differential diagnosis, or if susceptibility-weighted (T_2*) imaging or MR venography is not specifically requested. Patients presenting with what appear to be lobar hemorrhages on CT (young patients with temporal lobe hemorrhage especially) are particularly at risk of being misdiagnosed and mismanaged before the correct diagnosis is made.[19]

Hemorrhagic Stroke

CT scanning has generally been considered the investigation of choice for identification of intracranial blood; however MRI protocols including T2* imaging are now able to reliably detect acute cerebral hemorrhage, and are far superior to CT in the detection of subacute and chronic hemorrhage.[20–23] The sensitivity of T_2* and FLAIR MRI for the detection of acute subarachnoid hemorrhage is comparable with CT.[24]

Clinicians are already familiar with the need to make a specific diagnosis of the cause of hemorrhage, when it is detected. The development of catheter-based interventions for treatment of aneurysms and arterio-venous malformations (AVM) has meant that an even more detailed characterization of the size, morphology and anatomic location of these lesions is required to determine the appropriate therapeutic approach. Digital subtraction angiography (DSA) is generally required before final management decisions are made. MRI is very sensitive for the initial detection of AVM and other vascular abnormalities in the brain, including cavernous angiomata, which are often undetectable with DSA. MRA has a role in follow-up of any untreated lesions and screening of high-risk families.[25–27]

Specific diagnosis and management of ischemic stroke

Acute stroke

The NINDS trial[28] established the effectiveness of intravenous tissue plasminogen activator (tPA) for acute ischemic 'stroke' within 3 hours of symptom onset. While this is a major advance in stroke treatment, the advancement must not stop there. Thrombolysis according to the NINDS protocol adds one favourable outcome for every 13 patients treated, while causing harm to one in 17.[28] The NINDS trial and other negative multi-centre trials of intravenous thrombolysis[29–33] relied on a CT scan and a clock to characterize their patients before treatment decisions were made. This was appropriate at the time as other rapid methods of more detailed assessment were not generally available, but inevitably resulted in some patients being exposed to the risk of treatment without hope of benefit, such as patients whose vessels have spontaneously recanalized,[34] or those with little salvageable brain tissue within the hypoperfused region. At the same time, some patients who might benefit beyond 3 hours were denied treatment on the basis of time alone, not individual pathophysiological features.[35] The PROACT trials have subsequently demonstrated the potential of intra-arterial thrombolytic agents.[36,37] Occlusions of the internal carotid artery and proximal middle cerebral artery do not respond as well as more distal occlusions to intravenous thrombolysis, and may be better treated via the intra-arterial route.[37–39] Determining the appropriate applications for these potentially hazardous therapies requires a specific diagnosis.

More advanced, rapid, non-invasive imaging

techniques for assessment of acute ischemia are increasingly available. Multimodal stroke MRI protocols that include diffusion-weighted imaging, perfusion imaging, MRA and susceptibility-weighted imaging can be performed rapidly, exclude brain hemorrhage, define areas of hypoperfusion and tissue damage and identify occluded arteries, enabling decisions about thrombolysis to be made according to individual pathophysiological criteria.[34,35] DWI and MRA can enable an unequivocal diagnosis of acute stroke to allow stroke patients who might be excluded from thrombolysis on CT-based criteria to be treated, such as patients presenting with seizure at stroke onset, hypoglycemia or hyperglycemia. Definition of the 'ischemic penumbra' with diffusion and perfusion MRI may allow expansion of the therapeutic window beyond the current 3-hour guideline for selected patients.[35] Parameters are being established to identify those with an unacceptably high risk of hemorrhage due to the severity of the ischemic damage present at the infarct core.[40] Continued refinements in MR perfusion imaging techniques promise to allow more accurate predictions of the volume of brain tissue that is at risk of infarction if reperfusion does not occur, based on perfusion thresholds.[41]

In addition to enabling more specific application of thrombolytic therapies, physicians can use detailed knowledge of their patients' pathophysiology to select candidates for other acute stroke therapies. In particular, patients who are not candidates for t-PA but who have a persistent vascular occlusion and a significant volume of brain at risk of infarction due to tenuous collateral supply may benefit from hypertensive therapy to improve collateral circulation.[42]

Practical application of acute stroke MRI

Multimodal stroke MRI has been in use for several years in institutions in many countries, including our own hospital. The hardware and software required are increasingly available. Stroke fellows can be trained to perform the studies enabling 24-hour coverage independent of technician rosters. Acute hemorrhagic stroke can be accurately identified using an MRI protocol that includes susceptibility images, and additional CT scanning is not required before administering acute treatments.[20–22] Patients with multifocal small chronic hemorrhagic lesions due to presumed amyloid angiopathy can also be identified, who may be at increased risk of hemorrhage if thrombolytic agents are given.[23,43] The scanning time of an acute imaging protocol is less than 15 minutes. In the last 4 years at our institution, we have performed perfusion studies in over 300 acute stroke patients and have treated 29 acute stroke patients with t-PA on the basis of MRI results alone.

Stroke etiology and secondary prevention

A detailed diagnosis of stroke etiology is required to plan management strategies for secondary stroke prevention. This requires identification of the location and nature of the vascular lesions responsible, identification of systemic stroke risk factors and consideration of the likely pathophysiological mechanism of stroke. The elements of specific diagnosis of ischemic stroke are summarized in Table 1.2.

Diagnosis of vascular lesions

All levels of the vascular supply to the brain should be considered when determining stroke etiology, that is: the heart, aorta, proximal carotid or vertebral arteries in the thoracic cavity, cervical carotid and vertebral arteries and intracranial vessels. Not only must the anatomical location of vascular lesions be determined, but knowledge of the nature and severity of lesions is required, also. MRA can provide a comprehensive assessment of the vascular tree to determine the location and severity of vascular lesions. MRI with MRA is the non-invasive investigation of choice for the diagnosis and follow-up of carotid and vertebral artery dissection.[44] Duplex ultrasound remains more established than MRA for assessment of cervical internal carotid artery lesions, but promising results are being shown with contrast-enhanced MRA,[45] and vertebral artery assessment is superior with MRA. MRA has great promise in the evaluation of aortic lesions; [46] it is possible that in the future, MRI of the heart and great vessels will reduce the need for the

Table 1.2. Approach to ischemic stroke diagnosis

1. Initial ischemic stroke diagnosis:
   (a) stroke vs. non-vascular stroke mimic
   (b) ischemic stroke vs. hemorrhagic stroke vs. venous thrombosis
2. Acute stroke pathophysiology
   (a) severity and extent of ischemic brain injury
   (b) persistence and severity of cerebral hypoperfusion
   (c) identification of vascular occlusive lesion
3. Stroke etiology: vascular lesion
   (a) location of vascular lesion(s)
   e.g. cardiac, aorta, vascular origins, cervical vessels, intracranial vessels
   (b) nature of vascular lesion(s)
   e.g. cardiac: thrombus, AF, valvular, PFO, akinesis, endocarditis, other
   vascular: atherosclerosis – severity, ulceration, other high risk features
   other lesions – dissection, vasospasm, fibromuscular dysplasia, arteritis, drug-associated vasculopathy
4. Systemic stroke risk factors
   (a) traditional risk factor identification: hypertension, smoking, diabetes, hyperlipidemia.
   (b) thrombophilia
   acquired: antiphospholipid syndrome, polycythemia, thrombocytosis, hyperfibrinogenemia, other
   inherited: protein C, S, ATIII deficiency, prothrombin mutation
   (c) other, e.g. hyperhomocysteinemia
5. Stroke mechanism
   (a) embolic stroke
   (b) *in situ* thrombosis
   (c) lacunar infarction
   (d) hemodynamic / 'watershed' stroke
   (e) vasospasm
6. Stroke severity
   (a) clinical features, e.g. NIH Stroke Scale Score
   (b) lesion volume / location
7. Patient factors
   (a) premorbid functioning, age
   (b) comorbidities
   (c) psychological, social and economic factors

more invasive procedure of transesophageal echocardiography. Transcranial Doppler Ultrasonography is a useful method of assessing the major intracranial vessels but MRA or CTA offer the convenience of being performed at the same time as brain imaging. Digital subtraction angiography is still required when intravascular interventions are contemplated, on occasion to distinguish between critical stenosis and occlusion of the internal carotid artery, and to confirm the diagnosis of certain non-atherosclerotic vasculopathies, such as fibromuscular dysplasia, inflammatory and infectious arteritides, drug abuse-associated vasculopathy, and radiation-induced stenosis.

Specific vascular diagnosis and management

Cardiac-origin embolism

A full discussion of the diagnosis and management of cardiac-origin embolism is beyond the scope of this chapter and is available elsewhere.[47] Secondary prevention strategies can include anticoagulants, antiplatelet agents or their combination, antibiotics, antiarrhythmics and cardioversion, pacemaker, surgery, or catheter-based interventions. Therapeutic decisions depend on a specific diagnosis of the structural lesions involved and the likely composition of the embolic particle itself.[47,48]

Lesions of the aorta and great vessels

That the aorta is an important source of brain embolism is now well established.[49,50] The embolic risk is greatest for thick, complex and mobile plaques.[51,52] Gadolinium-enhanced MRA can establish this diagnosis quickly and accurately.[46] The best treatment to prevent embolism from aortic lesions is not yet known. Cases have been reported where aortic thrombotic masses have disappeared after anticoagulant therapy.[53,54] Intravenous thrombolytic treatment [55] and surgical removal of protruding atheromas[56] have also been reported to be successful in treating patients with aortic atheromas.

Atheromatous disease of the origins of the vertebral arteries is a common, yet often overlooked source of posterior circulation TIA and stroke.[57] Antiplatelet agents or anticoagulants are generally

the first line of treatment, but angioplasty and stenting of such lesions may sometimes be appropriate.[58]

Cervical vascular lesions

Carotid endarterectomy is well-established for the treatment of symptomatic severe (70–99%) internal carotid artery (ICA) stenosis.[59,60] The benefit of endarterectomy for symptomatic moderate (50–69%) stenosis is more modest and decisions about treatment must take individual and surgeon characteristics into account.[60,61] The benefit–risk ratio for carotid endarterectomy for unselected patients with asymptomatic ICA lesions is even lower[62] and treatment decisions must be individualized.[63,64] A significant increase in severity of stenosis increases stroke risk and favours surgery.[65] Identification of individual patients with higher stroke risk who would benefit most from surgical treatment may be possible using TCD microembolus detection,[66] or possibly platelet scintigraphy[67] or indicators of cerebral perfusion or vascular 'reserve'[68,69] including MRI perfusion techniques;[70] however, more studies are still required.[71]

Certain cervical carotid artery lesions may be better treated with intravascular interventions than traditional endarterectomy. Careful patient selection is required; indications might include high cervical lesions with difficult surgical access, radiation-induced stenosis, postsurgical restenosis, fibromuscular dysplasia and patients with high surgical risk due to severe medical comorbidity. A randomized controlled trial of carotid stenting and endarterectomy is planned.[72]

Dissection of the internal carotid artery generally does not require surgical intervention, even when aneurysms are associated;[73] however, patients may benefit from a period of anticoagulation.

Intracranial stenoses

The identification of intracranial stenoses can have important prognostic implications.[74,75] Whether anticoagulation is more appropriate treatment than aspirin for patients with intracranial disease is currently the subject of a multicentre randomized controlled trial.[76] Intracranial angioplasty and stenting, in the hands of experienced operators, may be beneficial for carefully selected patients with poor untreated prognosis refractory to medical therapy.[77]

Pathophysiological stroke diagnosis

Vascular imaging studies define the structural lesions important in stroke etiology, but may not show whether the stroke was due to thrombotic, embolic or hemodynamic mechanism, and do not inform about the nature of the embolic material itself. Some stroke subtypes, such as migrainous stroke, may not be associated with a structural vascular lesion. Clinical information must be combined with imaging data to achieve a specific diagnosis and tailor management for the individual patient.

Thrombosis and embolism

Our understanding of stroke pathophysiology has changed dramatically during recent years, emphasizing the importance of embolism in stroke pathogenesis.[47,48] The majority of non-lacunar ischemic strokes are likely to be embolic in origin. Secondary prevention strategy depends on identification of the donor source, risk factors, and consideration of the likely nature of the embolic particle itself.[47,48]

Thrombosis is likely when complete ICA occlusion is found, although even then embolism from the distal ICA thrombus may be the final stroke mechanism, and embolism from the heart may have caused the ICA occlusion.[78–80] Thrombosis may be an important mechanism when intracranial vascular stenoses are present. It may be difficult to know in some cases whether intracranial stenoses detected in the subacute period represent chronic lesions or partial recanalization of an embolus. Repeat imaging at a chronic time point with MRA, CTA or TCD may be required.

Hemodynamic stroke

The importance of hemodynamic factors as sole mechanism in stroke etiology has also been overemphasized in the past. Many strokes that may previously have been considered 'hemodynamic', particularly 'posterior borderzone' infarctions are likely to be caused by embolism.[81–84] However, impaired regional blood flow due to severe vascular stenosis or occlusion is likely to contribute to the

pathogenesis of embolic stroke. A small embolic vascular occlusion is more likely to result in infarction when insufficient collateral circulation is present, and low flow may impair clearance of emboli, or 'washout'.[85] Possibly the most reliable marker for hemodynamic infarction is the topographic pattern of infarction seen on acute multimodal MRI, including DWI, MRA and perfusion imaging, along with the appropriate clinical setting. Multiple small acute lesions are seen in widespread distribution within the internal borderzone region, in the absence of a vascular occlusion.[86] Evidence of a hemodynamic cause for stroke warrants consideration of reduction of antihypertensive medications or other measures to raise blood pressure, as well as consideration of revascularization procedures. Magnetic resonance perfusion and other methods of brain perfusion imaging such as SPECT, or TCD assessment of 'vascular reserve' may provide helpful information in the management of these patients in the future.[70,71]

Migraine and vasoconstriction

The diagnosis of migrainous stroke remains primarily clinical. Infarction can be caused by prolonged intense vasoconstriction[87,88] either directly as a result of impeded blood flow or due to secondary thrombosis.[88,89] Treatment for secondary prevention of migrainous infarction should include a migraine prophylactic agent as well as antiplatelet therapy. We have most often used verapamil in this setting.

Systemic stroke risk factors

Modifiable systemic stroke risk factors must be incorporated into the patient's diagnosis. Management must be individualized. Risk factors are not simply present or absent, but there is a continuum of increasing stroke risk with higher blood pressure and cholesterol levels.[90–93] The actual stroke risk may differ between individuals with the same blood pressure recordings, depending on how accurately recordings in the office reflect true daily levels, the duration of hypertension and the presence of additional risk factors. Evidence of significant end-organ damage such as extensive cerebral white-matter disease on CT or MRI scanning in a patient with apparently 'well-controlled' blood-pressure should prompt consideration of intensification of treatment. Ambulatory blood pressure recording may be very helpful to optimize the management in individual patients. The role of intensive lipid-lowering therapy in secondary stroke prevention is currently the subject of a large randomized trial.

Young patients and those without major vascular risk factors for stroke should also be tested for hereditary and acquired thrombophilic states (Table 1.2), the discovery of which can lead to modification of treatments prescribed, such as the use of higher intensity anticoagulation for patients with the antiphospholipid antibody syndrome,[94] or the introduction of additional treatments such as venesection for polycythemia, folate supplementation for hyperhomocysteinemia and use of agents such as eicosapentanoic acid (fish-oil) to reduce fibrinogen levels in hyperfibrinogenemia.[95,96]

Multiple possible causes of stroke

Some individuals presenting with stroke may have more than one potential cause identified. The major risk factors that predispose to atherosclerosis, such as hypertension, cigarette smoking, diabetes and hypertension promote plaque formation and occlusive disease in the coronary arteries, aorta and peripheral vasculature, as well as the craniocervical arteries.[97] Hypertension also predisposes the penetrating arteries of the brain to lipohyalinosis and atheromatous branch disease. The true frequency of multiple potential causes for stroke in the stroke population is not known. Variation in reported frequencies in the literature have been due to definitions used, such as the degree of carotid artery stenosis required before it is considered an etiological candidate, and how thoroughly the patients in each series were investigated. Improvements in diagnostic techniques will inevitably result in more such patients being identified.

Understanding of the activity of all of these processes in the individual patient is important. Data from the Lausanne Stroke Registry indicated that 46 (38%) out of 121 recurrent strokes had a different etiology than the initial index stroke.[98] In asympto-

matic carotid stenosis, 40% of strokes observed ipsilateral to severe carotid lesions were attributable to cardioembolic or lacunar etiologies.[99] In addition, the coexistence of coronary artery disease in patients presenting with stroke should not be overlooked. Patients who survive ischemic stroke face a similar risk of death from future myocardial infarction to that from recurrent ischemic stroke.[100]

Stroke severity

Stroke severity is an important diagnostic consideration in determining stroke prognosis, which in turn influences management decisions. Clinical features, which can be quantified using clinical scales such as the NIH Stroke Scale generally provide the most important prognostic information.[101] Early ischemic lesion volume detected with DWI is also an independent predictor of stroke outcome.[102] Imaging studies can be particularly important for prognosis in specific cases. The use of diffusion and perfusion MR imaging techniques and MRA in determining the prognosis of patients presenting with acute stroke has already been discussed. Detection of a large infarction involving the entire middle cerebral artery territory in a younger stroke patient is associated with a high risk of 'malignant' cerebral edema.[103] Large infarctions or hemorrhages in the posterior fossa may also be associated with the development of raised intracranial pressure.[104] Recognition of these patterns allows early discussion of treatment options that may include hematoma excision, hypothermia[105] and hemicraniectomy.[106]

Patient variables

Individualized stroke management requires consideration of the whole individual. Even once a specific pathophysiological diagnosis of stroke is achieved, other variables peculiar to that individual patient must also be considered before planning management. Pre-existent or coexistent illness may limit or affect treatment. The patient's premorbid function is also an important consideration. Age is never an absolute contraindication to stroke therapy, however elderly patients do not tolerate medical and surgical treatments as well as younger patients, nor do they rehabilitate as well from the effects of a stroke. Secondary prevention studies have demonstrated that the absolute benefit of treatments such as antihypertensive medication and carotid endarterectomy may be greater for elderly patients.[60,107] Socioeconomic and psychological factors may influence treatment decisions for some patients and their families.

Specific diagnosis and stroke patient management

The implications of the enormous heterogeneity of stroke and stroke patients for patient management should be obvious. Patients should be regarded as individuals and modern non-invasive imaging techniques should be used to obtain a specific diagnosis of stroke pathophysiology for each, in order to ensure optimal management. Acute stroke therapy should be offered when possible, preferably on the basis of pathophysiological, rather than arbitrary, criteria. All patients deserve assessment of potential risk factors, such as hypertension, diabetes, smoking, lifestyle, etc, and appropriate modifications should be instituted. The mechanism of stroke must be considered. Patients with atherosclerosis who have had evidence of cerebral ischemia should have an evaluation of their heart, coronary arteries, aorta and extracranial and intracranial arteries. When atherosclerosis is not the cause, a careful search for a specific alternative diagnosis must be made. Therapeutic strategies should then be instituted for each of the potential risks found and clinicians should carefully weigh the risk–benefit ratio of each strategy based on the totality of their knowledge of that individual patient. Some treatments such as antiplatelet medications or standard anticoagulants might be effective against more than one of the lesions found, while other treatments such as carotid endarterectomy or intracranial angioplasty are effective only for the lesions treated. Some treatments that should benefit one lesion (e.g. coronary artery bypass grafting) might pose a risk for patients with other lesions such as severe extracranial and intracranial occlusive disease.

Treatment decisions should be based on information gained about the individual patient, not on assumptions or arbitrary criteria. The availability of powerful non-invasive imaging technology makes thorough evaluation of each patient a realistic expectation. The increasing use of these techniques in randomized controlled trials will provide answers to important unresolved questions in stroke therapeutics and continue to improve outcomes for our patients.

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