Introduction: Approach to the patient

It happened on April 13, 1737, as "the whole house vibrated from a dull thud . . . something huge and heavy must have crashed down on the upper floor." The servant of the composer George Frederick Handel ran up the stairs to his master's workroom and found him "lying lifeless on the floor, eyes staring open . . ." Handel had come home from the rehearsal in a furious rage, his face bright red, his temples pulsating. He had slammed the house door and then stamped about, as the servant could hear, on the first floor back and forth so that the ceiling rebounded: it wasn't advisable, on such anger-filled days, to be casual in your service.

From the lower floor Christopher Smith, the master's assistant, went upstairs; he had also been shocked by the thud. He ran to fetch the doctor for the royal composer. "How old is he?" "Fifty-two," answered Smith. "Terrible age, he had worked like an ox." Dr. Jenkins bent deeply over him. "He is, however, strong as an ox. Now we will see what he can do." He noticed that one eye, the right one, stared lifeless and the other one reacted. He tried to lift the right arm. It fell back lifeless. He then lifted the left one. The left one stayed in the new position. Now Dr. Jenkins knew enough. As he left the room, Smith followed him to the stairs, worried. "What is it?" "Apoplexia. The right side is paralysed." "And will . . ."- Smith formed the words – "will he recover?" Dr. Jenkins laboriously took a pinch of snuff. He didn't like such questions. "Perhaps. Anything is possible."

This colorful excerpt from the famous story *George Frederick Handel's Resurrection* by Stefan Zweig illustrates a long-lasting dilemma for doctor and patient after an acute stroke: the question of diagnosis and prognosis.

Today, 260 years after George Frederick Handel's stroke, Dr. Jenkins' successors are better informed about the pathomechanisms involved in the acute situation, for example, ischemia vs. hemorrhage, cardio- and arterioembolic vs. hemodynamic sources of ischemia, or small-vessel vs. large-vessel disease. Even less common etiologies can be identified by additional tests (e.g., cerebrospinal fluid, biologic and immunologic tests). The benefits of acute therapy with a view to the different aetiologies have risen, and the prognosis can be more accurately estimated: Small cerebral hemorrhages or lacunar ischemic lesions have a good prognosis, both being related to chronic, often inadequately treated, hypertension

in patients with subcortical vascular encephalopathy; this was most likely the cause of Handel's stroke. We also have begun to elucidate the mechanisms of recovery after stroke. Functional magnetic resonance and studies with positron emission tomography have shown that, following ischemic damage to either cerebral hemisphere, residual connections to corresponding remote areas can be activated and that even new synapses and neural network transformations are possible. These new findings have updated previous misconceptions regarding lack of plasticity in the adult human brain. Many of these new techniques have limited the application of our nearly outdated traditional tests (e.g., conventional angiography).

Nevertheless, the clinical case still presents a challenge for our colleagues in medicine, whether they are students, residents or physicians with advanced expertise in stroke care. Like Dr. Jenkins generations of physicians and neurologists in particular have based their diagnosis on a combination of (a) *temporal profiles* of illnesses, and (b) the presence or absence of focal, symmetric, common, or uncommon *signs and symptoms* of stroke to conclude on the likely pathogenesis and pathobiology. The editors and contributors of this book have tried to crystallize a series of common and uncommon stroke cases and to discuss key elements, whether they are clinical, brain and vascular imaging derived or of other types of individual work-up. Beyond traditional concepts and performance, the actual principle "time is brain" or probably "penumbra is brain" for stroke patients is illustrated and consequently clinical evaluation, as well as technological studies are speeded-up, rather than traditional neurological examinations, a short but sufficient and therapy-related rather than diagnosis restricted repertoire is essential and includes all aspects of respiratory and cardiovascular function as well as scores of the level of consciousness (using the Glasgow Coma Scale, Fig. 1) and neurological and behavioral deficits (using the National Institutes of Health Stroke Scale, Fig. 2). Detailed investigation should be avoided, but medical and surgical history from patients and their relatives still are to be carefully considered with regard to previous stroke events, treatments for other cardiovascular diseases, etc.

Standard technical tests include:

(i) ECG
(ii) chest X-ray
(iii) blood sample studies/blood cell counts (including thrombocytes) glucose, creatinine, creatinin kinase or troponin, electrolytes, INR, APTT and toxic substance quinine.

An ECG should also be carried out because of the high incidence of heart conditions in this population. Stroke and myocardial infarction may occur

Glasgow Coma Scale			
	Best eye response	**Best verbal response**	**Best motor response**
5	—	Oriented	Obeys commands
4	Eyes open spontaneously	Confused	Localising pain
3	Eye opening on command	Inappropriate words	Withdrawal from pain
2	Eye opening to pain	Incomprehensible sounds	Extension to pain
1	No eye opening	No verbal response	No motor response
The GCS is scored between 3 (worst) and 15 (best) by adding the scores relating to each of three parameters: a score of ≥ 13 = mild brain injury, 9∝12 = moderate injury, ″ 8 = severe brain injury			

Glasgow Coma Scale

Glasgow Coma Scale	
Category	**Outcome**
1	Good recovery; independent lifestyle
2	Moderate disability; independent lifestyle
3	Severe disability; conscious but not independent
4	Vegetative state
5	Death

Figure 1 Glasgow Coma Outcome Scale.

together. Arrhythmias are frequently either the cause or the result of embolic stroke. Echocardiography should also be performed in most patients with stroke to document any cardioembolic source (thrombus in the left atrium or atrial septal aneurysm) or an atheroma in the arch of the aorta. Equally, an echocardiogram is necessary to detect a shunt of blood from the right to the left atrium through a patent foramen ovale or atrial septal defect. The accuracy of this ultrasound examination is greatly increased by transesophageal echocardiography and transcranial Doppler studies.

In the acute situation a separation between TIA and stroke is impossible and should not be accepted any longer not least as both prognosis and course of the disease are similar.

The same diagnostic studies are used for all patients with *brain attacks* whether ischemic or hemorrhagic are suspected: both groups need CT/MRI neuroimaging of the brain and vascular imaging including full cardiological work-up (Figs. 3 and 4).

CCT is the method of choice in both the acute and follow-up evaluation of cerebrovascular diseases, since its introduction in the early 1970s. Advantages of

NIH Stroke Scale

Assess level of consciousness

Alert	0
Drowsy	1
Stupourous	2
Coma	3

Assess orientation (month, age)

Both correctly	0
One correctly	1
Two incorrect	2

Follow commands
(1. Open and close eyes
2. Make fist and release)

Obeys both correctly	0
Obeys one correctly	1
Two incorrect	2

Follow my finger

Normal	0
Partial gaze palsy	1
Forced deviation	2

Visual field

Normal	0
Partial hemianopia	1
Complete hemianopia	2
Bilateral loss	3

Facial palsy
(Show teeth, raise eyebrows, squeeze eyes shut)

Alert	0
Drowsy	1
Stupourous	2
Coma	3

Motor strength for each of 4 limbs
(Passively move extremity and observe strength)
a. Elevate left arm to 90 degrees
b. Elevate right arm to 90 degrees
c. Elevate left leg to 30 degrees
d. Elevate right leg to 30 degrees

No drift	0
Drift	1
Some effort against gravity	2
No effort against gravity	3
No movement	4
Amputation, joint fusion (untestable)	9

Co-ordination of limb ataxia

Absent	0
Present in upper or lower	1
Present in both	2

Sensory
(1. Pin prick to face, arm, trunk and legs
2. Compare sides)

Normal	0
Partial loss	1
Dense loss	2

Speech clarity while reading word list

Normal articulation	0
Mild-moderate slurring	1
Nearly unintelligible, mute	2
Intubated or other physical barrier	3

Language (Describe picture, name items, read sentences)

No aphasia	0
Mild-moderate aphasia	1
Severe aphasia	2
Mute	3

Extinction and inattention

No neglect	0
Partial neglect	1
Profound neglect	2

Total

Figure 2 National Institute of Health Stroke Scale.

magnetic resonance imaging (MRI) are: excellent tissue contrast, high sensitivity for detecting early ischaemic and high susceptibility for demonstration of even very small haemorrhagic findings. Detection of flow parameters are excellent, although delineation of acute and developing penumbra surrounding the ischemic core or

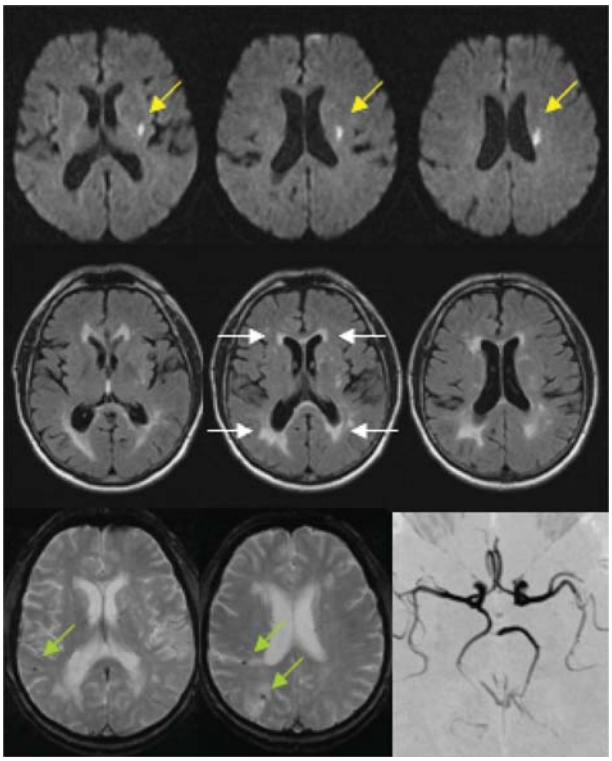


Figure 3 Typical MRI findings in a 78-year-old stroke patient with cerebral microangiopathy. Diffusion-weighted images (upper row) show a single hyperintense acute ischemic lesion in the territory of a perforating artery (arrow). The T_2-weighted FLAIR technique (middle row) demonstrates quite extensive chronic white matter lesions in a pattern typical for subcortical vascular encephalopathy with hyperintense lesions in the para- and periventricular white matter. T_2^* susceptibility-weighted sequences (bottom left and middle) show several small cortical/subcortical microbleeds, while the MR angiography (bottom right) demonstrates irregular contrast of intracranial vessels – a finding suggesting arteriosclerosis.

infarction are still insufficient as are sometimes developing ischemic territories close to parenchymal hemorrhage. Already approved early specific stroke treatment with tPA requires CT within a short 3 h time frame, potentially beneficial but not scientifically evaluated (or additional when using other drugs, including combinations of new protective and thrombolytic agents). Beyond this time limit, successful treatment can only be established if MRI or specific CT methodologies are used facilitating separation of perfusion deficits surrounding the core of already developing tissue necrosis (i.e., an equivalent of the ischemic penumbra).

Conventional angiography first performed in 1927, today is only selectively used in acute stroke patients, but is still considered for early interventional

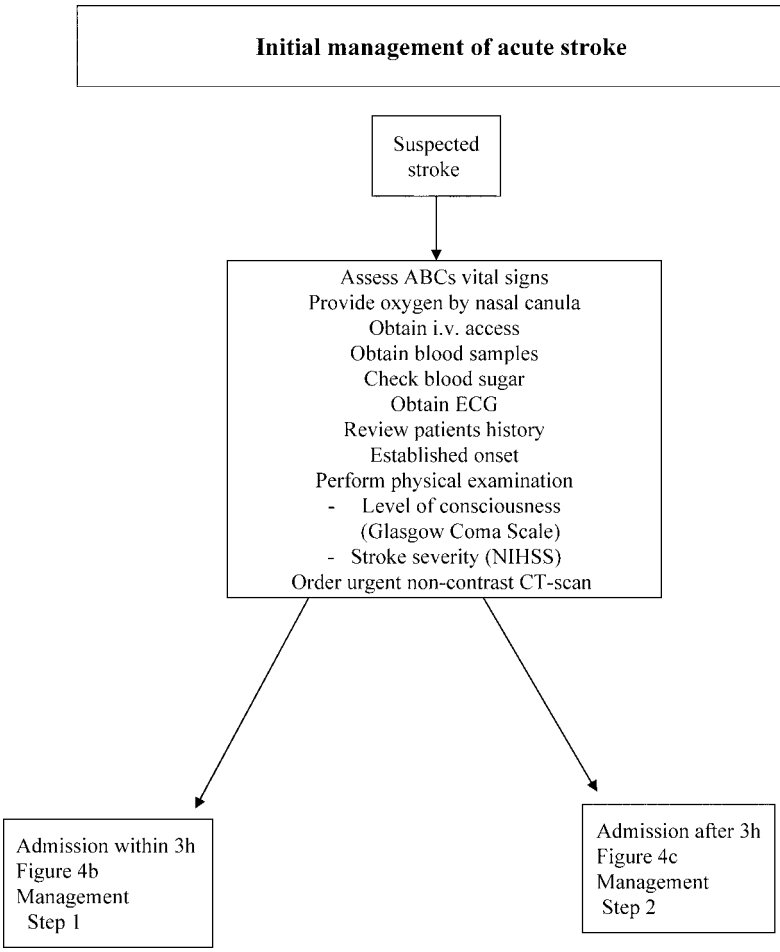


Figure 4a Initial management of acute stroke.

treatment. Despite encouraging and evidence-based results of intra-arterial thrombolysis in the carotid system in RCTs, indications for angiography are left to patients with basilar artery thrombosis and suspected vascular malformations and bleeding aneurysms. They either need immediate treatment during the diagnostic procedure itself or after previous MRA/CTA/ultrasound studies have suggested interventional rather than surgical conservative therapy planning. MRA and modern ultrasonography have overtaken large domains of catheter angiography and further technical and software development for refined analysis and online investigation will demonstrate preferential use and utility of such techniques in early stroke monitoring. In addition, treatment perspectives using MR/ultrasound technologies are on the horizon and have been studied already

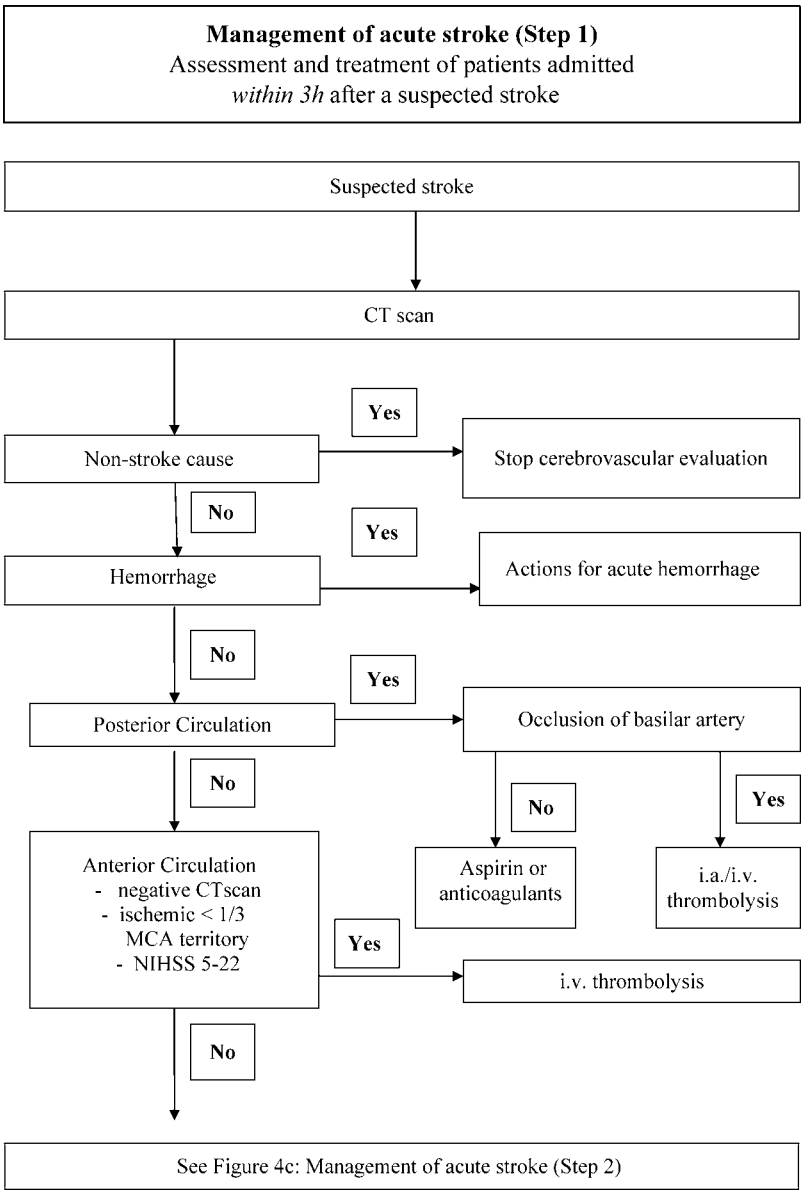
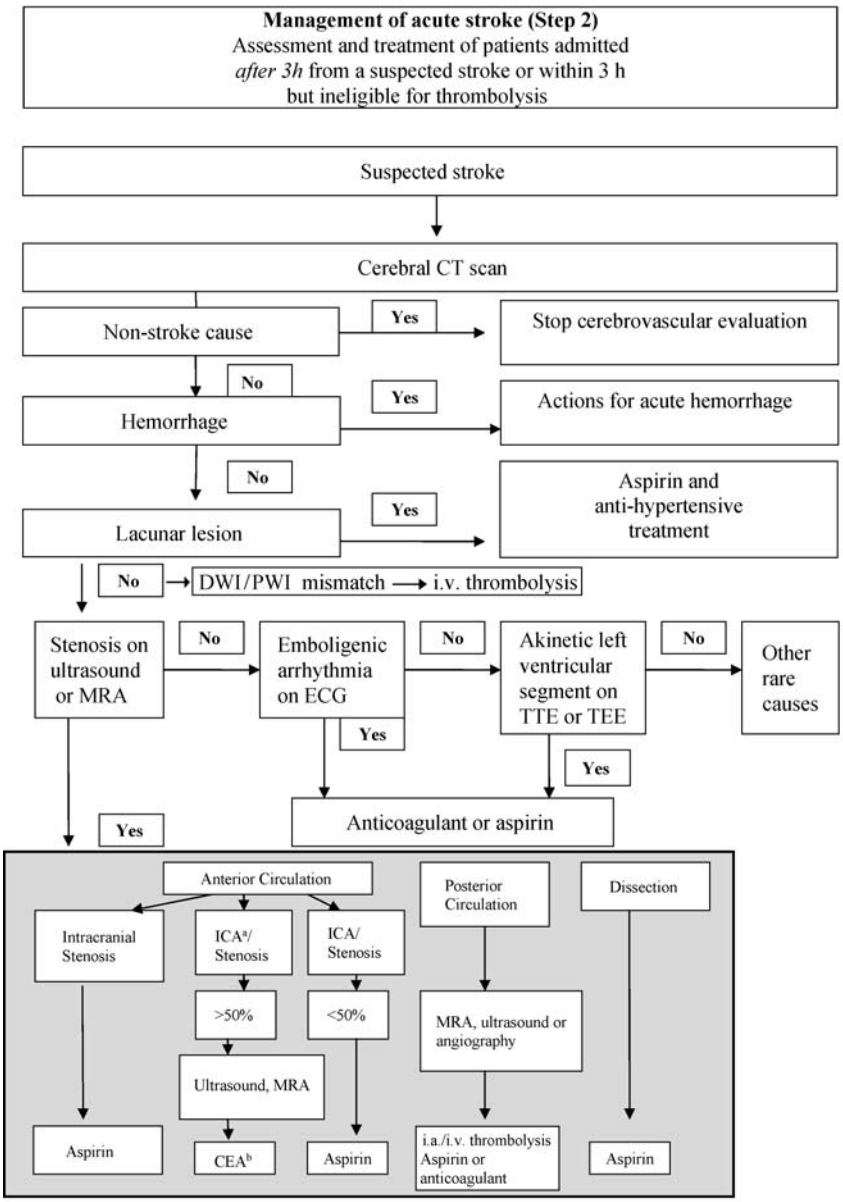


Figure 4b Management of acute stroke (Step 1).

in clinical trials. However, in patients with hemorrhagic strokes and subarachnoid hemorrhage that form 15%–20% of all stroke cases, conventional angiography will continue to represent the gold standard for diagnosis and increasingly for therapeutic interventions (e.g., coiling of aneurysms) as well or beyond neurosurgery.



[a]ICA, internal carotid artery, [b]CEA carotid endarterectomy, [c]TIA, transient ischemic attack

Figure 4c Management of acute stroke (Step 2).

The rapid development of non-invasive ultrasound techniques has resulted in a broad array of clinical applications for the assessment of both extracranial and intracranial arterial diseases, both in the acute and chronic conditions. Rather than providing information for the diagnosis and staging of various obstructive

cerebrovascular diseases, the capacity of ultrasound to identify and monitor continuously (on the ICU and Stroke Unit) and conditions of cerebrovascular circulation and brain perfusion in three dimensions and is preferential as well as the new application for sonothrombolysis. In addition, administration of microbubble encapsulated agents and drugs to selected focal areas within the brain by external destruction of their carrier demonstrates the perspectives of these techniques in acute stroke management.

Because of the advances in morphologic and functional neuroimaging, the diagnostic utility of electrophysiologic investigations, such as electroencephalography, and EP recordings have been dropped, reduced or even abandoned. However, these techniques still offer excellent chances for monitoring of brain functions of patients treated for complications and prevention of further brain tissue deterioration for the analysis of mechanism underlying clinical symptoms discrepant from neuroimaging findings. In particular, for the prognosis of functional outcome, they seem to provide far more relevant information than considered at present along with the best temporary resolution available and low cost. Sensory and motor EPs also are helpful in understanding mechanisms of recovery and reorganization in stroke patients and are indeed the only methodology at present to support a reliable prognosis.

Cardiovascular investigations on site and in close cooperation within the Stroke Team taking care of acute stroke patients are important for three major reasons: *first*, cerebral injury may force cardiac damage, even in patients without pre-existing cardiac disease; *second*, brain attacks may be cardioembolic in about 20%–30% of the cases and *third*, more than one-half of vascular patients may have co-existing coronary artery disease and the risk of coronary events with long-term follow-up exceeds the risk of cerebrovascular recurrences. While the last two reasons are commonly well considered, the first is still debated: knowledge on the pathophysiology of the autonomic system and the increasing number of patients with cerebral death as a possible donor for heart transplantations suggest that the cardiac consequences of cerebral damage is by far underestimated. Electrocardiographic monitoring has identified numbers of life-threatening ventricular arrhythmias in stroke patients treated on Stroke Units with continuous ECG monitoring and consequent treatment has rescued many of them from acute formerly suspected "stroke death." Acute cerebral damage may cause myocardial damage which can be documented by two-dimensional echocardiography, serum markers and myocardial necrosis; the clinical relevance of this is uncertain at present. Possible triggers of ventricular arrhythmia are hypoglycemia, hypoxia, autonomic nervous system imbalance and q-t prolongation; some of them can be promptly identified and adequately treated.

Biologic System	Test	Compartment	Method	Significance	Current Clinical Value
Glucose metabolism	Glucose (fasting, tolerance) HbA1c	Blood, urine plasma	Hexokinase method chromatography	Vascular risk factor, Diagnostic	Routine
Lipid metabolism	Cholesterol, triglycerides HDL/LDL-cholesterol	Blood	Enzymatic and precipitation techniques	Vascular risk factor	Routine
	Lp (a)	Blood	ELISA	Vascular risk factor	Routine
Methionine metabolism	Homocyst(e)ine	Blood, urine	HPLC	Diagnostic	Selected conditions
Antithrombotic systems	AT III, protein C, protein S	Plasma	Chromogenic assays, coagulometry	Diagnostic	Selected conditions
Coagulation and fibrinolysis	Prothrombin time, aPTT	Blood	Coagulometry, photometry	Therapy monitoring	Routine
	FM, FpA, TAT, F1+2 D-dimer, B-β-peptide	Plasma	ELISA	Pathogenic	Selected conditions
Systemic host defence	ESR, WBC, CRP	Blood serum	Westergren, impedance counter method, nephelometry	Investigation of acute phase reaction	Routine
	IL-6, IL-1β, TNF-α sICAM-1, sELAM-1, sL-selectin	Serum Plasma	Nephelometry, ELISA ELISA	Endothelial activation	Selected conditions
Viscosity of blood	Hematocrit, fibrinogen	Blood	Microhematocrit technique, coagulometry	Risk factor, pathophysiologic	Routine
	Whole blood, plasma viscosity, cell aggregability	Plasma	Filtration technique, shear-viscosimeter, aggregometer		Experimental
HPA system	Cortisol, ACTH	Plasma	RIA	Pathophysiologic Prognostic	Experimental
Immune system	ANA, anti-dsDNA Sm-Ag, Scl-70, ANCA	Serum	Immunofluorescence, RIA	Diagnosis of vasculitis (e.g. SLE)	Selected conditions
	Lupus anticoagulant / anticardiolipin Ab's	Plasma	Coagulometry ELISA	Pathogenetic	Selected conditions
Brain tissue integrity	NSE, S-100 protein	Serum, CSF	RIA	Prognostic	Selected conditions

Figure 5 Synopsis of Biologic and Immunologic Tests on Cerebrovascular Diseases.

Sources of cardioembolic stroke, whether from coexisting cardiovascular or cardiac diseases need to be diagnosed early and treated immediately to improve late prognosis, because of the coexistence of cerebrovascular and cardiovascular diseases in almost every second patient. A brain attack can be considered a "warning sign" for future coronary events and therefore should be of utmost importance in the network of secondary prevention.

A lumbar puncture for cerebral spinal fluid analysis is not necessary in the regular patient who presents with cerebrovascular disease; however, it may be indicated if intracranial hemorrhages are suspected (parenchymal and subarachnoid hemorrhages as well as cerebral venous thrombosis) or if forms of isolated angitis or systemic vasculitis with CNS involvement are considered. Biomarkers indicating neuronal damage, inflammatory reactions, apoptosis, or poststroke reorganization tissue-associated activities (e.g., superoxide dismotase) are currently targets of scientific interest; however, whether taken from the CSF or from