Diagnostic Procedures for the Selection of Patients at Risk for Stroke

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The third leading course of death after heart disease and cancer in industrialized countries is stroke. In Germany, it is estimated that more than 240,000 patients suffer a first stroke each year. Ischemic cerebrovascular disease may be divided into two categories, thrombotic and embolic. Although embolic strokes usually occur abruptly, they may present with fluttering, fluctuating, or transient symptoms, which are particularly obvious in patients with thrombotic strokes (50–75%). Atherosclerosis, arteritis, arterial dissections, hematologic disorders, and less frequent etiologies may all cause transient ischemic attacks or minor strokes, heralding a more devastating event if adequate diagnosis is not performed or secondary prevention fails. In addition, atherothrombotic arterial and cardiac sources of cerebral embolism need to be identified once a transient ischemic attack or reversible ischemic neurological deficit has occurred, or were identified by chance in patients presenting with signs and symptoms of atherosclerosis affecting noncerebral territories or with cardiac diseases (e.g., congenital heart diseases such as mitral valve prolapse and patent foramen ovale, acquired heart diseases following myocardial infarction, cardiac dysrhythmias such as atrial fibrillation, or infection).

Although transient ischemic attacks do not reflect the pathophysiology of cerebral ischemia but the presentation of signs and symptoms, their sequence of onset and disappearance may indicate the underlying pathogenesis:

(i) Large vessel transient ischemic attacks are usually brief (minutes or a few hours), recurrent, and stereotyped in the presence of a stenotic atherosclerotic lesion at the internal carotid artery origin or in the intracranial portion of the siphon, when collateral circulation through the circle of Willis is impaired. Similarly, stenotic lesions in the middle cerebral artery stem or at the junction of the vertebral and basilar arteries are predilective areas of obstructive vascular processes leading to a low flow syndrome, if collateral flow to the potentially ischemic brain is impaired (1).

(ii) Embolic transient ischemic attacks are usually single, prolonged (hours), and their features are often polymorphic. The embolus may arise from an extracranial...
or, less frequently, an intracranial artery or from the heart. Spontaneous resolution of the embolus is often associated with secondary clinical deterioration and fragmentation of the clot into distal arterial segments causing further ischemia within primarily nonaffected cerebral tissue. In addition, secondary hemorrhagic transformation may be found on brain imaging studies, even though clinically asymptomatic (2–4).

(iii) Lacunar or small penetrating vessel transient ischemic attacks are due to transient ischemia from proximal stenosis of intracerebral penetrating arteries (e.g., the deep penetrating lenticulostriate arteries from the middle cerebral artery and the circle of Willis and the penetrating branches to the brain stem from the vertebral and basilar arteries), or if small intracerebral penetrating vessels are occluded due to lipohyalinosis in patients suffering from chronic hypertension; they may be recurrent and stereotyped, as is for large vessel transient ischemic attacks (5).

DIAGNOSTIC TECHNIQUES

Several diagnostic techniques are available for the evaluation of patients at risk.

Noninvasive Diagnostics

Ultrasound represents the most accurate and frequently used noninvasive method for the direct assessment of structural and hemodynamic conditions in the extracranial carotid and vertebral systems. Color-coded duplex sonography represents the most recent developed technology, combining B-mode ultrasound imaging, range-gated pulsed Doppler flow-velocity assessment, and display of intra-arterial hemodynamics in cross and longitudinal sections. Transcranial Doppler of the circle of Willis and the major cerebral arteries (e.g., the middle, anterior, posterior cerebral arteries, as well as the intracranial vertebral and basilar arteries) is also useful and has been improved considerably by the addition of power imaging and harmonic imaging, using echo-contrast media. Extracranial ultrasound can detect atherosclerosis from its earliest stage (i.e., intima-media thickening) to total blockage and is as accurate as conventional angiography in the majority of patients selected for carotid endarterectomy. Transcranial duplex sonography is also becoming more accurate and diagnostically useful; however, insonation resistances in elderly women and black people with poor temporal bone windows prevent its use as a routine examination technique. Functional analysis of neurovascular coupling, cerebral autoregulation, arteriolar vasomotor reactivity in patients with suspected lacunar disease and display of high intensity transient signals (HITS) as potential indicators of silent cerebral microembolism are further rapidly improving techniques (6–8).

Cerebral Angiography

Conventional X-angiography, once representing the gold standard for the visualization of atherothrombotic disease, is now increasingly dispensed with following the
introduction and technical improvement of noninvasive methods. In particular, the combined use of ultrasound and magnetic resonance (magnetic resonance imaging, MRI; magnetic resonance angiography, MRA) have most recently reduced the need for selective extracranial conventional X-angiography drastically. Only in cases of disagreement between noninvasive studies and clinical results and for particular problems is it still needed. Detection of ulcerated lesions, severe stenosis versus occlusion, thrombus formation, dissection, and flow separation in the extracranial carotid and vertebral systems is now far better done with ultrasound than with conventional angiography.

Visualization of the course of the brain arteries in the carotid siphon and the posterior fossa can be performed by MRA.

Demonstration of collateral circulation in the circle of Willis and the major cerebral arteries can best be performed by intracranial ultrasound and MRA (9).

Brain Imaging

*Computed tomography* (CT) and MRI represent the most important tests for demonstration of ischemic territories and hemorrhage as a cause of stroke. Whereas CT is most frequently used in the acute situation, MRI and increasingly perfusion and diffusion imaging techniques are applied.

In contrast, *single positron emission tomography* (SPECT) and *positron emission tomography* (PET), although useful for the assessment for cerebral blood flow and metabolism qualitatively (SPECT) and quantitatively (PET), are not of any clinical importance because of the impracticability of the methodology and excessive cost and time-consuming natures of the techniques.

Cardiac Diagnostics

Echocardiography, ECG, and Holter monitoring represent standard investigations in patients at risk from stroke. *Transesophageal echocardiography* (TEE) has been shown to be superior to *transthoracic echocardiography* (TTE) and may be further improved by the application of echo contrast media for the detection of pathways of paradoxical embolism. The latter is also possible by contrast transcranial Doppler-duplex sonography without distressing the patients by the passage of an intra-esophageal tube (10).

Biological and Rheological Tests

Abnormal lipid metabolism, characterized by increased total cholesterol, triglycerides, low density lipoprotein, and decreased high density lipoprotein, is often associated with atherosclerosis and, despite a lack of evidence that reduction in serum cholesterol levels unequivocally results in reduced atherogenesis. Analysis of lipid
metabolism represents part of the routine workup in patients with cerebrovascular disease.

Lipoprotein (a), a low-density lipoprotein substance with an apolipoprotein (a) disulfide linked to apolipoprotein B 100, represents a more recent marker of atherogenesis, which is probably independent of the known risk factors for thrombogenesis. In addition, apolipoprotein E, chylomicron remnants, very low density lipoprotein, and high density lipoprotein have attracted increasing interest, although the association of these factors with cerebrovascular disease has still to be defined.

Abnormalities of methionine metabolism have long been thought to be rare conditions occasionally implicated in the pathogenesis of cerebral ischemia; however, heterozygous hereditary elevation of homocysteine and its metabolites, homocysteine and homocysteine-cysteine mixed disulfide, has increasingly been recognized as a potential risk factor for atherosclerosis, particularly in younger patients.

Analysis of the balance between coagulation and fibrinolysis (e.g., fibrin monomers, fibrinopeptin-A, prothrombin fragments F1 + F2, and TAT, the complex of thrombin and its inhibitor ATIII) are particularly important in cases where the etiology of transient ischemic attacks and RIND remains otherwise unknown. This is also true for protein C and protein S which, together with ATIII deficiencies, are responsible for disseminated intravascular coagulation.

Hemorheological tests (viscosity, hematocrit, erythrocyte aggregability, leukocytes size, rigidity, and adhesiveness to vascular endothelium) and indices of pre-existing infection and inflammation (ESR, white blood count, C-reactive protein, thromboplastin, or inflammatory cytokines) may be important not only as variables indicating an increased risk to stroke, but also in the pathogenesis of cerebral ischemia due to leukocyte-mediated neurotoxicity.

Inflammatory vascular diseases remain to be considered in the differential diagnosis of stroke of unknown etiology, although the percentage of acute strokes caused by them is small. Systemic lupus erythematosus, temporal arteritis, periarteritis nodosa, and Wegener’s granulomatosis should all be considered when routine inflammatory indices are positive without evident explanation or when history and clinical investigation suggest autoimmune vascular disorders. Lupus anticoagulants, a common cause of a prolonged activated partial thromboplastin time, and anticardiolipin antibodies are members of the group of antiphospholipid antibodies, which are less common causes of venous or arterial thrombosis.

REFERENCES


DISCUSSION

Dr. Bogousslavsky: I would like to know, with your expertise in this domain, whether you still perform a conventional carotid angiography before referring patients for carotid endarterectomy.

Dr. Hennerici: A consensus conference from many centers in Europe and the United States held in Paris last year concluded that in about 85% of patients, who are candidates for carotid endarterectomy, ultrasound and MR is sufficient and angiography can be avoided. It is only in a small proportion that angiography is necessary: either where the two noninvasive technologies provide different or contradictory results or where you need particular information on very small vessels.

Dr. Hossmann: I found it interesting that in vascular disease you may get a suppression of functional coupling. I refer to the case where you had a patient with atherosclerotic disease without any functional deficits, but apparently the blood flow did not couple to visual stimulation. We made similar observations after transient ischemia followed by reperfusion. Under these conditions, the EEG evoked potentials recovered but the functional activation of blood flow and metabolism did not recover, even though electrical physiological function recovers. I think this is a quite interesting and important observation because it raises the question of whether this technique could be used to study deficits of cognitive function.

Dr. Hennerici: It is certainly true that where the patient has already had some sort of ischemia, the one-to-one relationship between perfusion and metabolism may permanently be disturbed. This is much easier to demonstrate in the posterior circulation than in the middle cerebral artery territory because in the latter there is poor resolution of the ultrasound technique to the topographies. It is a promising field to explore.

Dr. Kleiser: How reliable is your three-dimensional technique when you compare alterations in the three-dimensional ultrasound with pathology?

Dr. Hennerici: There are some data available, mainly from two-dimensional sections, which indicate that as long as the lesion is small or not densified, you then have a very good correlation between the intraoperative specimen and the ultrasound scan. The angiogram is certainly less good if you do not consider ulcerated lesions smaller than 1 mm; the resolution borderline is about 2 mm for ultrasound in the detection of ulcerated lesions. Three-dimensional technology is much better because you can really turn the plug around, which is fairly difficult if you have a series of two-dimensional images, even if there are densifications or calcifications. Our experience is limited because of the small number of cases who finally go on to surgery: ulcerated lesions tend to heal nicely, so after a while, you see a nice cap on top of the lesion which you can identify much better in a three-dimensional image than is possible with a two-dimensional picture.
Dr. Stähelin: Have you tried to combine your intracranial techniques with functional MRI imaging in the affected areas?

Dr. Hennerici: We started this about 1 year ago. The problem is that functional imaging is a very nice technology for use in healthy volunteers who are prepared to spend an hour or two in the machine. It is much more difficult to study patients and, in particular, it is difficult to study patients in the vulnerable period after a stroke. We have done some very preliminary studies but I can't give you any definite results as yet.

Dr. Kornhuber: Does your method help us to understand why the branching of the carotid artery is such a sensitive area for the development of atherosclerotic plaques?

Dr. Hennerici: We know that this is histologically a very interesting area where changes of wall structure occur regularly. And we know that the anatomy of the branching vessels is also important for the initial atherosclerotic lesion. But what has not been addressed is what the wall characteristics are. We know from in vitro experiments that this is an area of recirculation where stasis occurs and where there is interchange of white blood cells and toxic substances with the endothelium, but the question still remains as to whether this is just a secondary phenomenon. Current interest is now focused on the examination of wall texture and motion, which is irregular and prominent in this area. The data support the concept of multiple causation of atherogenesis in this particular area; wall motion is not the only responsible variable but it is probably an important one.