In the first part of this article you have been provided with essential information about the pathophysiology and aetiology of cerebral infarction. This second part discusses the clinical diagnostic evaluation and treatment of this disease.

Clinical Diagnosis of Cerebral Ischaemic Infarction

Rapid and targeted diagnostic evaluation is essential in the clinical diagnosis of cerebral ischaemic infarction. According to the principle “time is brain”, clinical evaluation should be performed as a matter of urgency to initiate potential treatment without any delay. Cerebral infarction is a medical emergency and accordingly, patients with suspected cerebral infarction have priority in the emergency room!

Below, the diagnostic approach is described as it is suggested in clinical practice.

The clinical and neurological assessment of patients
with suspected cerebral infarction

Initially, a structured clinical neurological examination is necessary to determine whether focal neurological deficits exist and to identify the precise location of the area of infarction. The severity of a stroke (initial stroke severity) is assessed in the emergency department and, regularly thereafter, by means of the clinical stroke assessment tool NIHSS (= National Institutes of Health Stroke Scale).

Regular check-ups allow assessment of the dynamic pathophysiology of acute cerebral infarction and other potential complications, and also reveal the efficacy of intravenous thrombolytic therapy (see below).

Note: In many cases, a review of the patient’s medical history and a clinical neurological examination are sufficient to implicate the presence of a circulatory disorder. However, cerebral infarction cannot be distinguished with certainty from intracerebral haemorrhage on the basis of symptoms and signs alone!

Following the clinical neurological assessment of the patient, further emergency laboratory testing should routinely be performed. It is critical to select patients who qualify for thrombolytic therapy, by obtaining coagulation parameters before initiating the treatment.

Diagnostic radiology of cerebral infarction

Clinical neurological examination and blood tests are immediately followed by a CT scan of the head to exclude cerebral haemorrhage and to determine contraindications to thrombolytic treatment. Frequently, in addition to unenhanced CT brain scans, CT angiography (CTA) and CT perfusion imaging (CTP) are performed.

During the inpatient stay CT brain scans are used to monitor and to assess possible haemorrhage or the development of space-occupying lesions.

CT scans of the brain may be used to provide information on the following findings:

1. Early signs of cerebral infarction

Early ischaemic clinical signs are visible in the first 2 – 4 hours after the onset of the ischaemic event and may disappear after 12 – 24 hours. Early histopathological signs of a stroke are sulcal effacement with loss of grey-white matter differentiation. A visible hyperdense cerebral artery is the earliest ischaemic sign and is referred to as hyperdense posterior cerebral artery sign, and is apparent long before parenchymal changes.

Furthermore, also the delineation of the basal ganglia can be interpreted as an early sign of a middle cerebral artery infarction.

Note: Early signs of cerebral infarction do not arise directly after the onset of an ischaemic event! Patients presenting in the emergency department immediately after an ischaemic event, may have a perfectly normal CT scan!

2. Demarcated infarction

After the first 12 – 24 hours the infarcted tissue becomes sharply demarcated for example within a vascular territory. The affected area appears iso- or hypodense. Morphological findings weeks after an ischaemic infarction, include an area of definite hypodensity or a cystic cavity, which is often associated with signs of focal atrophy.
3. Fresh haemorrhage

Hyperdense space-occupying lesions detected by unenhanced CT can indicate acute haemorrhage.

4. Intracranial pressure

A large infarction or a stroke that causes the erosion of adjacent blood vessels, may cause the swelling of brain tissue (cerebral oedema), which in turn results in an elevation of pressure inside the skull. This may cause midline shift to the opposite side, causing a compression of ventricles. Raised intracranial pressure constitutes a severe neurological complication and is a call for urgent action!

For the evaluation of all patients with suspected cerebral infarction, in addition to the initial CAT scan, a MRI scan is required. MRI is useful specifically to identify microangiopathic lesions or arterial dissections with subintimal haematoma.

Furthermore, visualisation of the brainstem is much more precise by means of MRI, as the many surrounding osseous structures interfere with and limit CT scan resolution. Another advantage of MR angiography is that it does not require the administration of an intravenous contrast agent.

MRI plays another important part when it comes to the identification of patients who would benefit from intervention with thrombolytic therapies, once the critical ‘window of opportunity’ has already passed. To explain this, the following pathophysiological aspects should be considered: The irreversibly damaged cells form an infarct core. So called stunned cells with preserved integrity and metabolism are limited in their function, but can be saved in principle.

This area is called the ischaemic penumbra (= tissue at risk) and is an indication for thrombolytic therapy. By means of MRI, the infarct core can be differentiated from the penumbra via the concept of resonance perfusion-diffusion mismatch (PWI/DWI-mismatch).

Note: Abnormal cerebral MR perfusion measurements estimate the ischaemic penumbra,
while the infarct core is characterised by restricted diffusion. If the area with abnormal perfusion is larger than the area of restricted diffusion, this is called the ‘PWI/DWI mismatch’. The quotient of PWI/DWI measures the size of the tissue at risk.

Digital subtraction angiography (DSA) is used in the diagnosis of vascular disease and can help to confirm acute vascular occlusion. DSA provides comprehensive and accurate visualisation of the extra- and intracranial vasculature and can help clarify suspected vascular obstructions accurately.

**Transcranial Doppler ultrasonography examination of cerebral infarction**

Transcranial Doppler ultrasound (TCD) is another important diagnostic tool in acute stroke diagnosis. TCD provides information on cerebral blood flow velocity, the analysis of which allows physicians to draw conclusions on the presence of stenosis, emboli or potential vascular inflammation. TCD is also a useful tool for pre-surgical planning of ICA stenosis or for monitoring the efficacy of intravenous thrombolytic treatment.
Additional clinical investigations of cerebral ischaemic infarction

As part of inpatient primary care and in addition to the assessment of the actual infarction, a comprehensive aetiological investigation is performed. Doppler ultrasonography is one option. In addition, all patients will undergo ECGs and long-term ECGs, as well as (long-term) blood pressure measurements.

Also, echocardiograms will be performed in all patients. For the assessment of the individual cardiovascular risk, in addition to obtaining the medical history, also laboratory tests are carried out. In particular, information on lipid metabolism and blood glucose parameters should be obtained.

If these initial comprehensive medical investigations do not provide a coherent picture of both, clinical manifestation and aetiology, a broader diagnostic approach is required, to exclude or determine less common causes of cerebral infarction.

Differential Diagnoses: What Do I Have to Consider?

A range of other neurological disorders provoke and present with stroke-like symptoms. In any case, the exclusion of intracerebral haemorrhage has highest priority. Conditions with stroke-like symptoms are for example migraine with aura and scotomas, aphasia or even hemiplegia.

Also, epilepsy with auras or Todd’s paresis may mimic typical ischaemic symptoms. Other conditions in the differential diagnosis of ischaemic stroke include cerebral abscesses or primary CNS tumours.
Treatment Options of Cerebral Infarction

Each ischemic stroke requires priority emergency treatment, which must be performed as soon as possible in a dedicated ‘stroke-ready facility’, an emergency department that has the personnel and equipment to provide comprehensive acute stroke treatment and regular monitoring of the patients.

Emergency management of stroke patients involves regular neurological examinations to assess the pathophysiology of the disease and careful monitoring of physiological parameters, such as heart rate, oxygen saturation, blood pressure, temperature and blood sugar.

Basics of acute stroke treatment

The prognosis for patients with acute cerebral infarction is largely determined by comorbidities and vital signs. Emergency management of these patients is therefore essential for optimising the outcome after a stroke.

Optimal management of acute stroke patients should include:

**Respiration**

As brain tissue is under perfused, sufficient oxygenated arterial blood must be supplied. In case of major neurological deficits administration of 2 – 4 litres of oxygen/min may be considered. In brainstem infarctions with pathological breathing patterns or high risk of aspiration, endotracheal intubation must be considered.

**Arterial blood pressure**

Strong fluctuations of blood pressure must be avoided. Systolic blood pressure should be adjusted to 100 mm Hg and 180 mm Hg. Initially, elevated blood pressure values up to 220 mm Hg can be tolerated as the blood pressure usually normalises spontaneously.

Persistent hypertension above recommended levels should be lowered carefully, as it otherwise enhances the cerebral ischaemia. In these cases, administration of clonidine 0.15 mg s.c. or urapidil 5 – 25 mg i.v. is recommended. Hypotonic values must equally be avoided and, if necessary, intercepted with volume replacement or dopamine.

**Arterial blood pressure after thrombolytic treatment**

The rate for post-thrombolytic complications is lowest when the systolic blood pressure is kept < 180 mm Hg. Post-thrombolytic intracranial haemorrhage is the most concerning complication of acute stroke management, as it causes the most significant morbidity and mortality.

Elevated blood pressure values must therefore be avoided at all costs, however existing blood pressure therapies should not be stopped abruptly, instead they should be carefully adjusted.

**Glucose metabolism**

One can imagine that diabetics are often affected because of their pronounced cardiovascular risk profile. Diabetic metabolism may deteriorate massively in the context of a stroke. Hyper- and also hypoglycaemia can adversely affect stroke outcome. Therefore, blood sugar levels have to be adjusted! The recommended blood sugar target is 80 – 180 mg/dl.
Body temperature
Elevated body temperature increases the area of infarction. The recommendation is to lower the temperature from > 37.5 °C with antipyretic drugs (e.g. paracetamol).

Electrolyte balance
Maintaining an optimal fluid and electrolyte balance is important for regulating blood viscosity and cellular metabolism. Therefore, close clinical management and if necessary, a fluid and electrolyte therapy is indicated.

Systemic thrombolysis in ischaemic cerebral infarction
Intravenous thrombolytic therapy works by using a recombinant tissue type plasminogen activator (= rt-PA) to accelerate clot lysis. Once the obstructing thrombus has been dissolved, blood flow is restored. Thrombolysis shifts the equilibrium between clotting and bleeding (homeostasis) towards anticoagulation, affecting all organs in the body (= systemic).

Accordingly, the general risk of bleeding increases considerably, limiting the indication for thrombolytic therapy. The most important factor in successful thrombolytic therapy is early treatment. The sooner thrombolytic treatment begins, the greater the benefits for the patient. It should therefore be initiated promptly, as soon as a clear indication for thrombolysis has been established.

Absolute contraindications to thrombolytic treatment:

- Onset of symptoms more than 4.5 hours ago before start of treatment or if time of stroke onset is unknown. In these cases, the risk of haemorrhage into already potentially necrotic tissue is too high.
- Mild infarction or rapidly improving symptoms. The risk of thrombolysis outweighs the benefits.
- Severe heart attack (large infarction, early signs of infarction, vigilance impairment, hemiplegia within 3 hours).
- Impaired blood clotting due to disease (i.e. liver cirrhosis) or anticoagulation (warfarin, INR > b1,5).
- Current or recent infarction or haemorrhage.
- Major surgery within the last 3 months.
- Greatly increased and not manageable arterial hypertension (> 185/110 mmHg).
- Thrombocytopenia less than 100,000 mm3.
- Lumbar puncture within the last 7 days.

In addition to absolute contraindications, so-called relative, modifiable and potentially treatable contraindications to thrombolytic treatment are for example: brain tumours (malignancy), pregnancy, epileptic seizures, a recent traumatic brain injury (trauma) or disorders of glucose metabolism the risks and benefits of thrombolytic treatment must be considered individually.

Note: Antiplatelet drugs, a history of TIA or oral anticoagulation with an INR < 1.5 do not contraindicate systemic thrombolytic treatment.

Remember the following regarding the stroke thrombolysis protocol:

- I.V. rt-PA (0.9 mg/kg body weight, maximum dose 90 mg).
- With 10 % of the dose given as a bolus.
Remaining 90% followed by an infusion over 60 minutes.

The potential of interventional recanalisation

Intra-arterial thrombolysis by means of angiographic intervention is an alternative to systemic therapy. This technique is mainly used for the treatment of middle cerebral or basilar artery occlusions and can significantly improve the otherwise often infaust prognosis.

In addition to local intra-arterial thrombolysis and angiography also thrombectomy is a treatment option and, in principle also a stent can be used to provide structural support. After successful stenting, as in coronary heart disease, patients initially undergo a dual and later a simple antiplatelet therapy.

For a long time, the efficacy of interventional thrombectomy has been controversial and has not been scientifically verified. However, recent studies could demonstrate the benefit of these interventions for specific groups of patients.

Common indications for interventional thrombolysis with possible stenting are:

- Carotid T occlusion with imminent malignant media infarction. The risk of raised intracranial pressure and associated implications is very high and can be reduced by means of endovascular intervention.
- Unsuccessful systemic thrombolytic therapy.
- Diffusion perfusion mismatch beyond the actual thrombolytic ‘window of opportunity’.
- Contraindication to systemic thrombolytic treatment (e.g. pregnancy).
- Basilar artery occlusion may cause brainstem infarction. A variety of specific neurologic syndromes, for example the locked-in syndrome have been described in vertebrobasilar artery stroke. Recanalisation reduces mortality significantly and is even justified beyond the actual thrombolytic treatment window.

Secondary prevention

During hospitalisation early mobilisation should be enforced to reduce the risk of secondary complications, for example aspiration pneumonia, pressure ulcers or deep vein thrombosis. Following clinical evaluation, patients suffering from post-stroke dysphagia, should receive treatment options ranging from speech therapy to transnasal PEG tube placements.

Secondary bacterial infections must be treated and cured. Depending on the thrombosis risk parenteral anticoagulation should be initiated. In patients with post-stroke seizures or even epilepsy, an immediate pharmacological therapy should be considered.

The majority of diagnostic procedures is aimed at long-term secondary prevention to prevent recurrent ischemic stroke. In addition to optimising cardiovascular risk factors, causative underlying diseases must be identified and treated. Pharmacological and surgical treatment strategies depend on the hospital and the disease.

Treatment strategies of underlying diseases

Atrial fibrillation

Atrial fibrillation is a common, but also frequently asymptomatic (‘silent’) abnormal heart
rhythm. Accordingly, treatment and careful monitoring of affected patients is essential. The risk of stroke in atrial fibrillation is calculated by using the CHA2DS2 VASc score. The maximum CHA2DS2 VASc score is 9 points, indicating an increase in the annual stroke rate by 15 %.

A CHA2DS2 VASc score of ≤ 2 may be accompanied by an inhibition of platelet aggregation or may be associated with watchful waiting. It was found that in patients with atrial fibrillation at moderate to high risk of thromboembolic events (CHA2DS2 VASc risk score ≥2), oral anticoagulation (aiming for an INR between 2.0 – 3.0) significantly reduces the risk of ischemic stroke.

Table on the CHA2DS2-VASc score for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
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<tbody>
<tr>
<td>C</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>H</td>
<td>Hypertension</td>
</tr>
<tr>
<td>A2</td>
<td>Age (= over 75 years of age)</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>S2</td>
<td>Stroke (= history of ischaemic stroke or TIA)</td>
</tr>
<tr>
<td>V</td>
<td>Vascular disease</td>
</tr>
<tr>
<td>A</td>
<td>Fare (= over 65 years of age)</td>
</tr>
<tr>
<td>Sc</td>
<td>Sex category (= female)</td>
</tr>
<tr>
<td><strong>Maximum total score</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>

**Endocarditis**

Successful and appropriate treatment of endocarditis consists of targeted antibiotic therapy and eradication of infected areas (CVC, heart valves etc.). Even if thrombosis develops on a damaged heart valve, anticoagulation is not an option! The reason for this is frequent haemorrhage of existing infarction areas and the danger of thrombus detachment, i.e. the dreaded complication embolism.

Targeted antibiotic treatment of native valve endocarditis involves a combination of ampicillin, gentamicin and cefotaxime/ceftriaxone. For the treatment of endocarditis involving a prosthetic heart valve, a combination of vancomycin, gentamicin and rifampicin is recommended. Successful antibiotic treatment is dependent on the identification of the causative pathogen.

**Arterial dissection**

The treatment of dissections of brain-supplying arteries is an exception. Despite involvement of the arterial territory, standard anticoagulation or alternatively administration of antiplatelet drugs is recommended. Recanalisation is uncommon in vessels with occlusion.

**Treatment of ICA stenosis**

ICA stenosis, like almost all atherosclerotic vascular changes, has been associated with a specific cardiovascular risk factor profile. Accordingly, aggressive management and optimisation of cardiovascular disease risk factors is an essential part of treatment.

Affected patients should reduce their weight, arterial hypertension must be well-adjusted, smoking cessation should be strongly encouraged and if necessary, cholesterol should be lowered. For primary prevention platelet aggregation inhibitors (e.g. aspirin 100 mg
1.0.0) are administered, which reduces the annual cerebral ischaemic stroke risk significantly and should therefore be suggested to all patients.

There is a debate, whether ICA stenosis should be treated surgically or by interventional therapy. The risk-benefit ratio of these options must be carefully considered. The following basic rules are helpful reminders for everyday life and in exams alike:

The treatment of ICA stenosis is determined by clinical presentation and degree of blockage.

- Symptomatic patients with stenosis ≥ 70 % receive surgical or interventional treatment.
- Both, invasive and interventional treatment is considered beneficial in symptomatic patients with stenosis between 50 % and 70 %.
- Patients with low-grade carotid artery stenosis of less than 50 % do usually not undergo surgery or receive interventional treatment.
- Asymptomatic patients with high-grade carotid artery stenosis tend to be treated more conservatively.
- After interventional treatment, antiplatelet therapy (initially dual) is recommended.
- Antiplatelet therapy reduces the long-term risk of stroke after surgical intervention and should therefore be initiated and continued post-surgery.

Note: Frequent is often and is therefore also frequently queried. Remember the ICA stenosis treatment regimen!

Clinical Consequences of Cerebral Infarction

Surely it has become evident, that cerebral infarctions exhibit a wide diversity of clinical signs and symptoms. It is the same when it comes to the consequences of a stroke. Everything, between complete remission and persistence of clinical signs and symptoms is possible. In principle, all stroke patients have access to neurorehabilitation services.

Rehabilitation interventions, such as physiotherapy, occupational therapy or speech therapy are commonly initiated during inpatient care and are continued after discharge if indicated. Thereby, long-term neurological impairment may be reduced, to facilitate functional recovery, i.e. improvement in mobility and activities of daily living.

Review Questions

The answers can be found below the references.

1. Which of the following rehabilitation interventions should be avoided during acute care of stroke patients?

   A. Oxygen administration at a flow rate of 2 - 4 L/min.
   B. Cautious treatment of markedly elevated blood glucose levels.
   C. Drug-induced rapid lowering of elevated blood pressure to low/normal levels.
   D. Slight head-of-bed elevation.
   E. Lowering of elevated body temperature.

2. You work in the neurological emergency department and are confronted with the following case: 67-year-old man, known arterial hypertension, patient alert, oriented, responds adequately when addressed, follows requests as far as
motor skills permit, shows no gaze palsy, no visual field defect, no sensory impairment and no neuropsychological disorder however, paresis of the right arm and leg and drooping of the mouth on the right side. Which of the following vascular pathologies is the most likely?

A. Left lacunar cerebral infarction  
B. Left epidural hematoma  
C. Left dorsolateral medullary infarction  
D. Hypertensive haemorrhage in the right basal ganglia  
E. Dorsal midbrain syndrome

3. An 81-year-old patient has been diagnosed with atrial fibrillation. He suddenly develops paresis predominantly of the distal foot and leg, as well as a speech defect. After an hour, his speech has completely recovered, while the distal foot and leg paresis is persistent. Which of the following diagnoses is the most likely in this case?

A. Brainstem ischaemia in subclavian steal syndrome  
B. Posterior cerebral artery territory infarction  
C. Migraine with brainstem aura (basilar-type migraine)  
D. Acute middle cerebral artery infarction  
E. Cardioembolic stroke in the region supplied by the anterior cerebral artery (anterior cerebral artery syndrome)

4. Mr. Friedrich had a thromboendarterectomy of the internal carotid artery. He states that prior to this operation, he continually suffered from short-term episodes of blindness, which made him feel extremely anxious. When asked, Mr. Friedrich explains that these episodes were not accompanied by further symptoms, for example dizziness. How the visual impairment Mr. Friedrich describes best is referred to?

A. Bitemporal hemianopia  
B. Homonymous hemianopia  
C. Horner’s syndrome  
D. Amaurosis fugax  
E. Internuclear ophthalmoplegia

References

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Masuhr, K. F., Neumann, M., Duale Reihe Neurologie, Thieme, 2007

Correct answers: 1C, 2A, 3E, 4D

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