Stroke in Young Adults
in Northern Sweden

Bo Traberg Kristensen

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ABSTRACT

Stroke in Young Adults in Northern Sweden

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Objectives. To study different aspects of cerebral venous and arterial occlusive disease including cerebrospinal fluid hydrodynamics, epidemiology, aetiology, genetics, metabolic and haemostatic disorders, and cognitive function in young adults in Northern Sweden.

Methods. Cerebrospinal fluid hydrodynamics were investigated with a constant pressure infusion method in patients with superior sagittal sinus thrombosis. Ten patients were studied with serial examinations, up to 15 years after the onset of the disease.

Epidemiological data on ischaemic stroke in young adults aged 18 to 44 years were collected to calculate incidence and mortality based on the WHO Northern Sweden MONICA register of acute stroke events. One hundred and seven consecutive patients aged 18-44 years with ischaemic stroke referred to Umeå university hospital were studied prospectively during a five-year period and were extensively evaluated according to a standardized protocol. During follow-up at least three months after onset 102 and 80 patients, respectively, were evaluated for disturbances in the fibrinolytic system and in the metabolism of homocysteine. A comprehensive neuropsychological battery was performed in a subset of 20 patients with infratentorial infarcts.

Results and conclusions. All patients with superior sagittal sinus thrombosis demonstrated a marked increase in intracranial pressure due to raised pressure in the sagittal sinus. A striking feature was the persistent intracranial pressure increase with only a slow decline over time.

The incidence rate for ischaemic stroke was higher than previously reported from most countries in Western Europe. The higher incidence was not explained by a higher prevalence of atherosclerotic vasculopathy. In spite of extensive evaluation, including advanced cardiac imaging, the cause of ischaemic stroke in young adults still remains uncertain or unknown in most cases.

Patients had lowered tissue plasminogen activator activity and increased plasminogen activator inhibitor type 1 activity. Increased fibrinogen levels and tissue plasminogen activator mass concentration were independently associated with ischaemic stroke. Metabolic perturbations were closely interrelated with tissue plasminogen activator and plasminogen activator inhibitor type 1 activity. Elevated plasma fibrinogen levels and abnormalities in the fibrinolytic system in conjunction with metabolic perturbations may be important contributors to an increased stroke risk among young adults.

Stroke patients had an exaggerated increase in total homocysteine levels after methionine loading. Abnormal responsivity to methionine loading was associated with higher tissue plasminogen activator mass concentration, plasminogen activator inhibitor 1 levels and lower tissue plasminogen activator activity. Abnormal homocysteine metabolism may provide an additional thrombogenetic risk, partly mediated by interactions with the fibrinolytic system.

Circumscribed infratentorial lesions (mainly cerebellar) impaired central aspects of attention and working memory, and inflicted damage upon visuospatial skills. In contrast, these patients may not suffer from global intellectual impairment and difficulties with respect to memory for previous events. The prognosis is favorable in terms of neurological deficits and handicap, but cognitive disability may be the most significant problem in adapting to their former occupations.

Key words. Cerebral venous thrombosis, cerebrospinal fluid dynamics, ischaemic stroke, young adults, epidemiology, fibrinolysis, homocysteine, cerebellar infarct, neuropsychology.
From the Departments of Clinical Neuroscience and Medicine, University of Umeå, Umeå, Sweden.

Stroke in Young Adults in Northern Sweden

Bo Traberg Kristensen

Umeå 1998
To Helle, Mette, Kamilla and Mia

Men under tiden
Flyr den oersättliga tiden

Vergilius
# Contents

Abstract ............................................................................................................ 7  
Original papers .................................................................................................. 9  
Abbreviations .................................................................................................. 10  
Introduction ...................................................................................................... 11  
Cerebral venous thrombosis ........................................................................ 13  
  Superior sagittal sinus thrombosis ................................................................. 15  
  Cerebrospinal fluid hydrodynamics ................................................................. 16  
Arterial thrombembolic stroke .................................................................... 16  
  Epidemiology and aetiology ......................................................................... 16  
  The fibrinolytic system ................................................................................. 17  
  Fibrinogen and von Willebrand factor ........................................................... 20  
  Homocysteine ............................................................................................... 21  
  Cognition and cerebellum ............................................................................. 25  
Objectives ........................................................................................................ 30  
Patients and controls ...................................................................................... 31  
Methods ........................................................................................................... 35  
Results .............................................................................................................. 41  
Discussion ......................................................................................................... 49  
  What to do and when to do it ....................................................................... 59  
Conclusions ....................................................................................................... 66  
References ........................................................................................................ 68  
Acknowledgement ............................................................................................ 83  
Original papers .................................................................................................. 85  
  Paper I ............................................................................................................ 89  
  Paper II .......................................................................................................... 99  
  Paper III ....................................................................................................... 109  
  Paper IV ....................................................................................................... 127  
  Paper V ....................................................................................................... 147
Abstract

**Objectives.** To study different aspects of cerebral venous and arterial occlusive disease including cerebrospinal fluid hydrodynamics, epidemiology, aetiology, genetics, metabolic and haemostatic disorders, and cognitive function in young adults in Northern Sweden.

**Methods.** Cerebrospinal fluid hydrodynamics were investigated with a constant pressure infusion method in patients with superior sagittal sinus thrombosis. Ten patients were studied with serial examinations, up to 15 years after the onset of the disease.

Epidemiological data on ischaemic stroke in young adults aged 18 to 44 years were collected to calculate incidence and mortality based on the World Health Organization Northern Sweden MONICA register of acute stroke events. One hundred and seven consecutive patients aged 18-44 years with ischaemic stroke referred to a university hospital were studied prospectively during a five-year period and were extensively evaluated according to a standardized protocol. During follow-up at least three months after onset 102 and 80 patients, respectively, were evaluated for disturbances in the fibrinolytic system and in the metabolism of homocysteine. A comprehensive neuropsychological battery was performed in a subset of 20 patients with infratentorial infarcts.

**Results and conclusions.** All patients with superior sagittal sinus thrombosis demonstrated a marked increase in intracranial pressure due to raised pressure in the major dural sinus. A striking feature was the persistent intracranial pressure increase with only a slow decline over time.

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plasminogen activator and plasminogen activator inhibitor type 1 activity. Elevated plasma fibrinogen levels and abnormalities in the fibrinolytic system in conjunction with metabolic perturbations may be important contributors to an increased stroke risk among young adults.

Stroke patients had an exaggerated increase in total homocysteine levels after methionine loading. Abnormal responsivity to methionine loading was associated with higher tissue plasminogen activator mass concentration, plasminogen activator inhibitor type 1 levels and lower tissue plasminogen activator activity. Abnormal homocysteine metabolism may provide an additional thrombogenetic risk in part mediated by interactions with the fibrinolytic system.

Circumscribed infratentorial (mainly cerebellar) infarctions impaired central aspects of attention and working memory, and inflicted damage upon visuospatial skills. In contrast, these patients may not suffer from global intellectual impairment and difficulties with respect to memory for previous events. The prognosis after cerebellar infarctions is favorable in terms of neurological deficit and handicap, but cognitive disability may be the most significant problem in adapting to their former occupations.
The thesis is based on the following papers, which will be referred to in the text by their Roman numerals:


<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>aCL</td>
<td>Anticardiolipin antibodies</td>
</tr>
<tr>
<td>APC</td>
<td>Activated protein C</td>
</tr>
<tr>
<td>ASA</td>
<td>Atrial septum aneurysm</td>
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<tr>
<td>BI</td>
<td>Brainstem infarct</td>
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<tr>
<td>CI</td>
<td>Cerebellar infarct</td>
</tr>
<tr>
<td>CIP</td>
<td>Coagulation inhibitory proteins</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computerized tomography</td>
</tr>
<tr>
<td>ICA</td>
<td>Internal carotid artery</td>
</tr>
<tr>
<td>ICD-9</td>
<td>International Classification of Diseases, 9th Revision</td>
</tr>
<tr>
<td>MONICA</td>
<td>Monitoring trends and determinants in cardiovascular disease</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MTHFR</td>
<td>Methylenetetrahydrofolate reductase</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiography</td>
</tr>
<tr>
<td>Gop</td>
<td>Conductance of the cerebrospinal fluid outflow pathways</td>
</tr>
<tr>
<td>PAI-1</td>
<td>Plasminogen activator inhibitor-1</td>
</tr>
<tr>
<td>Pcl</td>
<td>Cerebrospinal fluid resting pressure</td>
</tr>
<tr>
<td>Pdop</td>
<td>Pressure difference across the cerebrospinal fluid outflow pathways</td>
</tr>
<tr>
<td>PFO</td>
<td>Patent foramen ovale</td>
</tr>
<tr>
<td>PLP</td>
<td>Pyridoxal-5-phosphate</td>
</tr>
<tr>
<td>Pss</td>
<td>Sagittal sinus pressure</td>
</tr>
<tr>
<td>qf</td>
<td>Cerebrospinal fluid formation rate</td>
</tr>
<tr>
<td>tHcy</td>
<td>Total homocysteine</td>
</tr>
<tr>
<td>SSST</td>
<td>Superior sagittal sinus thrombosis</td>
</tr>
<tr>
<td>TEE</td>
<td>Transesophageal echocardiography</td>
</tr>
<tr>
<td>TOAST</td>
<td>Trial of ORG 10172 in Acute Stroke Treatment</td>
</tr>
<tr>
<td>TTE</td>
<td>Transthoracic echocardiography</td>
</tr>
<tr>
<td>tPA</td>
<td>Tissue plasminogen activator</td>
</tr>
<tr>
<td>VA</td>
<td>Vertebral artery</td>
</tr>
<tr>
<td>VO</td>
<td>Venous occlusion</td>
</tr>
<tr>
<td>vWF</td>
<td>von Willebrand factor</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
Although one is never too young to be affected by a stroke, the lower and upper limits of age that define a young adult with stroke are rather arbitrary. By convention the age span in this situation is usually set in the range of 15–18 years up to 45–50 years of age. The separation is useful and justified by differences in aetiologies, evaluation and prognosis in this younger population as compared with stroke in the elderly.

In contrast to arterial occlusion in the cerebral circulation, cerebral venous thrombosis typically affects younger adults. More than 50% of the cases with cerebral venous thrombosis are younger than 40 years whereas young adults account for less than 5%–10% of arterial occlusions (1–2). Despite a long history of thrombotic occlusion of the cerebral veins and sinuses, first described post–mortem in man by Ribes (1825), little is known about this disease as compared with our knowledge concerning arterial stroke.

Although the incidence of stroke involving the arterial system is much lower in patients aged 18–45 years than in patients older than 45 years, it is not uncommon for neurologists to encounter stroke in the young, particularly at a tertiary referral center. In this young adult age range ischaemic stroke is a relatively common neurological disorder, with an incidence higher than that of multiple sclerosis (3–4). Establishing the diagnosis and cause of stroke in the young is often a challenging task. While some causes in the young are similar to causes of stroke in the elderly, the causes of ischaemic stroke among young adults are more diverse than during later life. Up to 120 causes of stroke in the young have been listed, and the need of a thorough diagnostic evaluation of these patients is obvious (9). The topic of ischaemic stroke in young adults has received increasing attention in recent years, and many have reported series of cases describing the relative frequencies of risk factors and presumed aetiology (Table 1)(5–14).

Previous studies addressing the aetiology of ischaemic cerebral infarction in the young have often been retrospective with data gathered from chart review, with highly variable investigational techniques, and variable diagnostic criteria (15). In addition, advances in technology, including transesophageal echocardiography and new biochemical assays, have introduced new potential causes of ischaemic stroke which still need to be substantiated.
Atherosclerotic large artery disease (9-48%)
≥ 50-60% stenosis or ulcerated plaque or
two or more atherosclerotic risk factors

Non-atherosclerotic disease large or
medium-sized artery disease (10-33%)
Carotid or vertebral dissection
Fibromuscular dysplasia
Angitis

Cardioembolism (7-35%)
Congenital heart disease
Infective endocarditis
Valvular disease
Patent foramen ovale and interatrial
septal aneurysm

Penetrating artery disease (3-18%)
Lipohyalinotic and atherosclerotic
Small vessel vasculitis

Prothrombotic states (8-15%)
Antiphospholipid antibody syndrome
CIP deficiency
Disorders of fibrinolysis
Activated protein C resistance (Factor V mutation)

Miscellaneous (1-20%)
Migraine (2-15%)
MELAS
CADASIL
Homocystinuria

Undetermined (cryptogenic) (7-40%)

TABLE 1. POTENTIAL CAUSES OF ISCHAEMIC STROKE IN YOUNG ADULTS ACCORDING TO THE
LITERATURE. Abbreviations: CIP, coagulation inhibitory proteins; MELAS, mitochondrial encephalopathy, lactic
acidosis and stroke-like episodes; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and
leucoencephalopathy.

Seven to 40% of young patients with stroke have an undetermined or unknown
aetiology despite extensive diagnostic evaluation (16–18). It is therefore important to
identify new and potentially treatable risk factors and to gain further insight into the
pathogenetic mechanisms. Since most stroke resources are designed to meet the
needs of the elderly, they may fail the small but significant proportion of younger
people. Recent studies have suggested that prognosis, including the ability to return
to work, is less favourable than has been reported previously (19). In part, physical
impairment may explain this, but little attention has been paid to cognitive deficits
and their influence on prognosis in terms of residual disability and handicap. The
cognitive impairment imposed by a stroke deserves further attention, and
neuropsychological studies in these patients provide a unique opportunity to
scrutinize the effects on cognitive function from ischaemic lesions in different anatomic sites of the brain. The concept of a cerebellar contribution to cognition has begun to attract attention and dysmetria of movement has been equated in the cognitive realm with "dysmetria (or ataxia) of thought" (20). Hence, studies of previously healthy individuals with well defined and isolated lesions of the cerebellum and brainstem are of major interest.

CEREBRAL VENOUS THROMBOSIS

Cerebral venous thrombosis is a relatively rare condition, and before the introduction of serial angiography it was impossible to diagnose during life. The greatly increased diagnostic precision afforded by angiography and more recently by magnetic resonance imaging has enabled complete and partial thrombosis of the cerebral veins and sinuses to be recognized with increasing ease and frequency. In spite of increasing awareness, cerebral venous thrombosis is still a disease in which the correct diagnosis is frequently overlooked or delayed, because the wide spectrum of clinical presentations both in terms of the speed of onset and the range of symptoms. The unique part played by the arachnoidal villi of the superior sagittal sinus in the circulation of cerebrospinal fluid makes intracranial hypertension a cardinal feature of venous thrombosis at this site.

Anatomy

The cerebral veins contain 70% of the total cerebral blood volume, and are arranged in a superficial and a deep venous system. The venous sinuses are enclosed between the fibrous layers of the dura mater, and are located at junctions and edges of the falx cerebri and the tentorium cerebelli (Figure 1). They receive tributaries from the superficial and deep venous systems as well as from the cranial vault via a system of venous lakes within the skullbones. The superior sagittal sinus drains the major part of the blood from the cerebral hemispheres. Most of the cerebral venous blood flows posteriorly and drains via the sigmoid sinuses into the jugular veins.

Pathophysiologcal aspects

There are two main factors that determine the outcome of venous occlusion: the availability of preexisting collateral venous channels and the extent to which the thrombus propagates along the veins. Aside from venous infarction, one of the main effects of venous thrombosis is interference with cerebrospinal fluid (CSF) circulation.
The occurrence of intracranial hypertension usually indicates thrombosis of the superior sagittal sinus causing impaired CSF absorption either from blockage of arachnoid granulations (Figure 2) by a thrombus or from chronically raised venous pressure. Blockage of the free bulk flow of cerebrospinal fluid at the arachnoid granulations by the thrombosis leads to an increase in CSF pressure. A severe breakdown of the blood–brain barrier with an increase in brain water content occurs only when the superficial cortical veins or bridging veins are also occluded (21). The development of edema further increases the intracranial pressure. Following vein occlusion, preexisting collateral venous channels often show a progressive enlargement acting as collaterals. These veins have a characteristic morphology and can be recognized on angiography as delicate spiral structures running in the cerebral white matter, constituting the transcerebral venous system and usually draining into the deep cerebral venous system.
Superior sagittal sinus thrombosis

Superior sagittal sinus thrombosis (SSST) (Figure 3) is the most frequent form of aseptic cerebral venous thrombosis. Age and sex distribution show a peak incidence in the third decade and a female/male ratio of 1.3 – 1.5 (22–23). When thrombosis is restricted to SSST, the clinical presentation is that of isolated intracranial hypertension and papilloedema is frequently observed (24). In contrast to arterial thrombosis, the thrombotic process may continue for several days, weeks or even months. Extension of thrombus formation to cortical veins is frequent and is characterized by the acute or progressive onset of a focal motor or sensory deficit associated with focal or generalized seizures. Acute onset may mimic subarachnoidal haemorrhage or arterial stroke. There are many underlying causes but none is found

<table>
<thead>
<tr>
<th>Prothrombotic states</th>
<th>Systemic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puerperium</td>
<td>Bechets’ disease</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Lupus anticoagulans</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>Wegener’s granulomatosis</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td></td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haematologic</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential thrombocythaemia</td>
<td>Carcinomatous meningitis</td>
</tr>
<tr>
<td>Polycythaemia vera</td>
<td>Arterio-venous fistula</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Homocystinuria</td>
</tr>
<tr>
<td>Acute lymphatic leukemia</td>
<td>Head injury</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

TABLE 2. SOME CAUSES OF PRIMARY (ASEPTIC) CEREBRAL VENOUS THROMBOSIS.
in 25% of the cases (Table 2). The mortality probably does not exceed 10%, and only about 20% of survivors are left with sequelae (25). The survivors generally recover clinically but in a cohort of 77 patients with SSST, 12% suffered a second cerebral venous thrombosis, all but one within the first year of follow-up (26).

Cerebrospinal fluid hydrodynamics

Simple lumbar cerebrospinal fluid (CSF) pressure measurements have been reported from patients with venous sinus pathology (27). In clinical routine lumbal puncture has become obsolete in many cases since the advent of MRI, but it is still useful in cases with isolated intracranial hypertension and to measure and rapidly decrease CSF pressure in emergency situations. The opening pressure is usually elevated (> 2 kPa or 15 mm Hg), and the cerebrospinal fluid profile depends on the underlying functional disorder. CSF hydrodynamics have been studied by direct intra-sinal and intraventricular pressure measurements in individual patients under special circumstances, such as during anaesthesia (28) or neurosurgery (29). Serial investigations and fundamental pathophysiological changes in CSF hydrodynamics in SSST over time have not been reported.

ARTERIAL THROMBEMBOLIC STROKE

Epidemiology

The incidence rates of ischaemic stroke are only known by approximation, since they require very large studies or regional registries, that each have their specific shortcomings. For instance, even the largest studies will have considerable statistical uncertainty, hospital registries do not include individuals who died before admission, and statistics based on death certificates suffer from misclassified diagnoses. The age-specific incidence of stroke among individuals in the young age-group has been reported by community and hospital surveys from various geographical areas (Table 3). However, hardly any population-based data have been reported (30).

Aetiology

The aetiology of ischaemic stroke affects prognosis, outcome, and management. An aetiology-specific classification of ischaemic stroke is useful in studies of the epidemiology and pathophysiological basis of stroke. The Trial of ORG 10172 in
Population source

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Stockholm, Sweden (130)</th>
<th>Gothenburg, Sweden (131)</th>
<th>Denmark (132)</th>
<th>Reggio Emilia, Italy (133)</th>
<th>Firenze, Italy (30)</th>
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<tbody>
<tr>
<td>1973-77 n=154</td>
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<td>15-44</td>
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<td></td>
</tr>
<tr>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
<td>0</td>
<td>0.9*</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>n.a.</td>
<td>8.4</td>
<td>0.9*</td>
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<tr>
<td>10</td>
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<td>n.a.</td>
<td>15.6</td>
<td>8.2*</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>9.9</td>
<td>8.0 [4.7-12.8]</td>
<td>3.4 [2.0-5.4]</td>
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</tr>
</tbody>
</table>

TABLE 3. AGE SPECIFIC INCIDENCE RATES OF ISCHAEMIC STROKE IN THE YOUNG (PER 100 000).
NOTE THAT THE PRESENT STUDY INCLUDED PATIENTS IN THE AGE INTERVAL 18-44 YEARS.
Abbreviations: n.a = not available; # age group 15-34 years; * age group 35-44 years; [95% confidence interval].

Acute Stroke Treatment (TOAST) classification classifies subtypes of ischaemic stroke using clinical features and the results of ancillary diagnostic studies. "Possible" and "probable" diagnoses can be made based on the physician’s certainty of diagnosis. The TOAST stroke subtype classification system is also easy to use and has a good interobserver agreement (31).

An aetiologically based classification has been further developed from the TOAST classification in the context of ischaemic stroke in young adults with explicit definitions of the major accepted categories of ischaemic stroke. Fair to good reliability for this classification has been obtained (32), and with slight modifications this classification system was chosen for our studies (See page 43).

The fibrinolytic system

In order to maintain haemostatic equilibrium the endothelium furnishes an antithrombotic milieu by secretion of compounds such as protein S and tissue-type plasminogen activator (tPA) but also produces compounds promoting clot formation, such as von Willebrand Factor (vWF), and plasminogen activator inhibitor 1 (PAI-1) (33). A schematic illustration of the intravascular fibrinolytic system is shown in Figure 4.

THE RELATIONSHIP BETWEEN tPA AND PAI-1

Whereas antigen levels refer to the total amount of the circulating proteins (both bound and free), activity levels refer to the functionally active portions of the proteins. tPA and PAI-1 activity can be determined by functional assays, while immunological assays measure the total amount of tPA, i.e., tPA mass concentration (previously often named tPA antigen). The tPA mass concentration assay also measures the inactive
STROKE IN YOUNG ADULTS

Endothelium

Liver uptake

PAI-1

t-PA

plasminogen

plasmin

FDP

fibrin-platelet thrombus

\( \text{vWF} \)

FIGURE 4. SCHEMATIC ILLUSTRATION OF THE INTRAVASCULAR FIBRINOLYTIC SYSTEM. Fibrinolysis denotes the proteolytic degradation of polymerised fibrin by plasmin, which in turn is generated from plasminogen by plasminogen activators, in order to prevent thrombus formation. The proenzyme plasminogen is synthesised in the liver and is converted to plasmin under the influence of tissue plasminogen activator (tPA). The vascular endothelium synthesises, stores and releases tPA and is considered to be the main source of circulating tPA. The fibrinolytic activity in blood is determined by the concentration of active tPA. In healthy man approximately 20% of circulating t-PA is free and biologically active. In addition to the circulating tPA protein, tPA also binds to the endothelial wall via a specific receptor or via bound PAI-1. The ratio between these two may determine the anti-thrombogenic character of the vessel wall. The main inhibitor of t-PA in plasma is PAI-1 and thereby acting as a major regulator of fibrinolytic activity by inhibiting t-PA. The cellular origin of PAI-1 is unknown. Synthesis of PAI-1 in vivo has been demonstrated in endothelial cells, smooth muscle cells, hepatocytes and recently in adipocytes. It is found in plasma, platelets and extracellular matrix. Adapted from: Wall U, In vivo studies on local release of tissue-type plasminogen activator from vascular endothelium, University of Gothenburg, 1997 (PhD Thesis).

complex formed by tPA and PAI-1 in addition to measurement of the free active fraction of tPA (Figure 5). Therefore, tPA mass concentration is not, in a conventional sense, an assay of fibrinolytic activity. This is probably because an elevated tPA mass concentration most often reflects a high level of circulating PAI-1, resulting in a large proportion of the tPA being bound to PAI-1 and thereby rendered inactive.

SAMPLING PROCEDURES

Due to circadian rhythms of fibrinolysis the time-point of sampling must be well standardized and morning samples after an overnight fast are recommended (34). Minimal stasis and rest before venipuncture is mandatory. To maintain tPA activity between sampling and analysis, blood should immediately be collected in tubes.
containing a strong acidic citrate anticoagulant to prevent PAI-1 from inactivating tPA. Studies that did not use this technique (before 1990) will have reported invalid and far too low measurements of tPA activity (35).

It has been suggested that assessing fibrinolytic response to venous occlusion can give valuable information on fibrinolytic potential and capacity (36-37), but the biochemical mechanism of these changes and their clinical meaning is still unclear.

**THE FIBRINOLYTIC SYSTEM AND VASCULAR DISEASE**

The concept that impaired fibrinolysis is a risk factor for future cardiovascular disease is supported by prospective studies in which endogenous fibrinolytic capacity assessed at baseline was found to predict future rates of cardiovascular morbidity and mortality.

This concept has been demonstrated for healthy men at risk for future myocardial infarction (38), and stroke (39). In contrast, the role of the fibrinolytic system in cerebrovascular disease has received less attention, and only a few studies have considered these aspects of haemostasis in a young stroke population with contradictory results (Table 4).

Variables evaluated have included antigen levels for both tPA, and its primary inhibitor, PAI-1 as well as PAI-1 activity. Depending upon what factors are controlled for, the relative importance of tPA and PAI-1 as predictors of thrombotic risk varies. This observation is not surprising since correlations have been described between fibrinolytic variables and several lipid, behavioural, metabolic and inflammatory markers (40-41). PAI-1 levels are thus strongly associated with the cluster of variables included in the "insulin resistance syndrome" (42), such as increased body mass index, and plasma insulin, high triglyceride and low HDL cholesterol levels. tPA antigen is also related, as well as PAI-1, to the numerous variables belonging to this cluster of cardiovascular risk factors.
Table 4. Earlier studies of the fibrinolytic system in young adults with ischemic stroke.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients / Controls</th>
<th>Baseline fibrinolytic variables</th>
<th>VO-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>tPA ac</td>
<td>tPA mc</td>
</tr>
<tr>
<td>&lt; 45 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke type: Infarct/TIA</td>
<td>TA, &gt; 6w</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TP, n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baumgartner et al, 1988 (120)</td>
<td>21 / 13</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>Stroke type: Infarct/TIA</td>
<td>TA, 10 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TP, 12-14 pm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chancellor et al, 1989 (121)</td>
<td>38 / 19</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>Stroke type: Unexplained aetiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TA, 36 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TP, n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 55 years</td>
<td>119/80</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Mettlinger et al, 1982 (122)</td>
<td>Stroke type: Minor stroke and TIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TA, &gt; 3 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TP, 730-1030 am</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke type: Premature atherosclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TA, n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TP, n.s.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 4. EARLIER STUDIES OF THE FIBRINOLYTIC SYSTEM IN YOUNG ADULTS WITH ISCHAEMIC STROKE.** Abbreviations: n.s., not stated; n.d., not done; n.a., not applicable; mo, months; TIA, transitory ischemic attack; VO, venous occlusion test; ac, activity; mc, mass concentration. ↑ increased; ↓ decreased; → no difference. TA, time of analysis after stroke onset; TP, time-point of sampling.

**FIBRINOGEN AND VON WILLEBRAND FACTOR**

Circulating fibrinogen levels increase with age, obesity, high circulating cholesterol and triglycerides levels, increased blood pressure and cigarette smoking. High levels of fibrinogen may predispose to thrombosis by producing a hypercoaguable state, accelerate the development of atherosclerosis, and reduce blood flow through effects on plasma viscosity, erythrocyte aggregation and leucocyte activation (43). Two prospective observational studies (44-45) and two case–control studies (46-47) have suggested that fibrinogen is an independent risk factor for stroke in the elderly.
population, but the role of high plasma fibrinogen levels as a risk factor for ischaemic stroke in young adults has not been studied in detail.

Von Willebrand factor (vWF), produced by the vascular endothelium, promotes platelet adhesiveness to exposed endothelium following vessel injury. Data from a recent case-control study indicated that elevated vWF, sampled in most cases several months after the event, should be considered a risk factor for transitory ischaemic attack and minor stroke (48). However, this association was not confirmed in a prospective study (49). The relationship of this variable to ischaemic stroke in young adults has not been studied.

Homocysteine

HOMOCYSTEINE METABOLISM AND TERMINOLOGY

Homocysteine (Hey) is a sulfur-containing amino acid derived from the metabolic conversion of methionine. Its intracellular metabolism occurs through enzymatic pathways that are dependent on vitamins as cofactors (Figure 6).

![Figure 6: Methionine/Homocysteine Metabolism in Man](image)

FIGURE 6. METHIONINE/HOMOCYSTEINE METABOLISM IN MAN. There are two pathways of remethylation of homocysteine to methionine. In that catalyzed by methionine synthase, the methyl group is donated by methyltetrahydrofolate and cobalamin acts as a cofactor. In the other pathway, betaine is the methyl donor and the reaction is catalyzed by betaine-homocysteine methyltransferase. In the transulfuration pathway, homocysteine is transformed by cystathionine-b-synthase into cystathionine, with pyridoxal-5'-phosphate (PLP), the biologic active form of vitamin B6, acting as a cofactor. Abbreviations: MS, methionine synthase; MTHFR, methylenetetrahydrofolate reductase; BHMT, betaine-homocysteine methyltransferase; CBS, cystathionine-b-synthase; Cbl, methylcobalamin; B6, vitamin B6 (pyridoxal-5'-phosphate).
Homocysteine is oxidized in plasma to the disulfides homocysteine–homocysteine (homocystine) and homocysteine–cysteine (mixed disulfide). Homocysteine and the two disulfides exist both in free and protein–bound forms. Only a very small fraction of Hcy in the reduced form is present in plasma as non–protein–bound. 70–80% is bound to albumin, and the remaining 20–30% forms disulfides. The sum of all the forms is referred to as total homocysteine (tHcy). The chemical structures of Hcy and related substances are shown in Figure 7.

HYPERHOMOCYSTEINEMIA

If one or more of the Hcy metabolizing pathways are inhibited due to enzymatic defects or vitamin deficiencies, Hcy accumulates, thereby causing an increased tHcy level in plasma. The diagnosis of hyperhomocysteinemia is usually based upon the measurement of the plasma levels of tHcy by high pressure liquid chromatography with electrochemical or fluorescent detection (50). The cutoff point for hyperhomocysteinemia is usually set at the 90th or 95th percentile of the homocysteine distribution of healthy subjects or more than 2 SD above the mean. Normal fasting plasma tHcy concentrations in adults has been reported to range typically from 5 to 15 μmol/L (51).

Mild hyperhomocysteinemia occurs in approximately 5–7% of the general population (52–53). Measurement of plasma homocysteine after a standardized oral methionine load to stress methionine/homocysteine metabolism improves distinction of normal individuals from subjects with mild abnormalities of homocysteine metabolism (54–55). Relative to the fasting level, the postmethionine load tHcy and the increase in tHcy (the difference between fasting and postmethionine load tHcy levels) measured after 4 to 6 h are usually about 3 and 2 times higher, respectively (55). The tHcy response induced by protein–rich food may represent the physiologic corollary of the methionine load (56). Enzymes in the transsulfuration pathway are responsible for reversing transient postprandial increases.

FIGURE 7. CHEMICAL STRUCTURES OF HOMOCYSTEINE AND RELATED SUBSTANCES.
HYPERHOMOCYSTEINEMIA IN STROKE

Data from about 80 epidemiological and case-control studies have shown that both basal and post-methionine load levels or net increments above fasting levels of tHcy are associated with increased risk for atherothrombosis (57–58).

The natural history of various inborn errors of Hcy metabolism, collectively termed homocystinuria, demonstrates that severe hyperhomocysteinemia is a strong risk factor for vascular disease, the chance to suffer from thromboembolic events under the age of 30 years for untreated patients being as high as 50% (59). On autopsy, the macroscopic findings include arteriosclerotic findings in large and medium sized arteries. However, fatty atheromatous plaques in the arteries are not a common finding (60).

Recently, a mutation in the methylenetetrahydrofolate reductase (MTHFR) gene, the most common inborn modification of folate metabolism, has been suggested as a new candidate risk factor for vascular disease (61). The prevalence of homozygosity for this C677T mutation (TT genotype) varies between 5% and 20% (a corresponding allele frequency of about 40%) in subjects of Caucasian descent (62). A functional consequence of this gene modification is a thermolabile enzyme with decreased activity. The increased prevalence of the homozygous mutant genotype in cardiovascular disease has been supported by some, but not most studies. Recently the association of C677T mutation of MTHFR and the risk for stroke in an elderly population was not confirmed (63). The possible role for the MTHFR mutation as a risk factor for stroke in a young population has not been studied.

Apart from these genetically based defects in methionine/homocysteine metabolism, it is now obvious that non-genetical factors such as dietary-induced vitamin B deficiencies and renal dysfunction also lead to hyperhomocysteinemia. There is also a positive relationship between tHcy and several of the conventional risk factors such as total cholesterol, smoking and high blood pressure.

Since the first controlled study on homocysteine plasma levels in patients with a history of stroke (64), it has been shown that hyperhomocysteinemia is associated with an increased rate of ischaemic stroke, independently of classical risk factors (65–71). By pooling the data up to 1994, mild postload hyperhomocysteinemia was detected in 24% of patients with cerebrovascular disease and 2% of the control subjects (72). The prevalence of fasting hyperhomocysteinemia in stroke cohorts has varied between 23% to 42% (73). In a recent meta-analysis of 27 studies published before 1994, summary odds ratio calculated from fasting homocysteine levels only, yielded an odds ratio for cerebrovascular disease of 2.5, 95% confidence interval 2.0 to 3.0 (57). Four recent prospective studies, however, observed contradictory results concerning vascular events: hyperhomocysteinemia was either a strong and independent risk factor for stroke (74) or myocardial infarction (75), was a small but not significant risk factor for stroke (76), or was without any association at all with stroke (77) or myocardial infarction (78).

Only a few case-control studies have previously provided more detailed information with respect to homocysteine metabolism in patients with cerebrovascular
disease under the age of 55 years, whereas no previous study has studied young adults with ischaemic stroke below the age of 45 (Table 5) (55, 66, 69, 79-80).

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases/Controls (no.)</th>
<th>Time of analysis</th>
<th>Type of measurement</th>
<th>Elevated Hcy (%) Cases/ Controls</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boers &lt; 50 y (66)</td>
<td>25/40</td>
<td>&lt;4-6 wk</td>
<td>Peak PML</td>
<td>28/0</td>
<td>Included 8 TIA</td>
</tr>
<tr>
<td>Brattström &lt; 55 y (79)</td>
<td>35/46</td>
<td>Months-years</td>
<td>Fasting tHcy and PML increase</td>
<td>17* - 24‡/4</td>
<td>Also TIA</td>
</tr>
<tr>
<td>Clarke &lt; 55 y (69)</td>
<td>38/27</td>
<td>ns</td>
<td>Peak PML</td>
<td>42/0</td>
<td>Included 6 TIA; 47% with carotid occlusive disease</td>
</tr>
<tr>
<td>Dudman &lt; 61 y (80)</td>
<td>51/56</td>
<td>ns</td>
<td>Peak PML</td>
<td>23/0</td>
<td>CVD not specified</td>
</tr>
<tr>
<td>Graham &lt; 60 y (55)</td>
<td>211/800</td>
<td>&lt;12 mo</td>
<td>Fasting tHcy; peak PML; PML increase</td>
<td>34.6/20; 41.2/20; 36.5/20</td>
<td>Atherosclerotic CVD; TIA included</td>
</tr>
</tbody>
</table>

TABLE 5. SUMMARY OF STUDIES ON HOMOCYSTEINE (Hcy) AND YOUNGER PATIENTS WITH ISCHAEMIC CEREBROVASCULAR DISEASE. Abbreviations: TIA, transient ischemic attack; CVD, cerebrovascular disease; mo, months and PML, postmethionine load test. * CVD on the basis of carotid artery disease. Significant differences from controls for both basal homocysteine concentrations and post-methinine increases. ‡ CVD defined as cerebral thrombosis. Differences from controls non-significant for both basal homocysteine concentrations and post-methinine increases.

MECHANISMS OF INDUCED VASCULAR DISEASE

The mechanisms by which hyperhomocysteinemia contribute to atherogenesis and thrombogenesis are incompletely understood. Homocysteine has been found to be damaging to endothelial cells in a number of experimental animal and cell culture studies (81-83). It has been demonstrated in primates that diet–induced hyperhomocysteinemia leads to impaired vasomotor regulation in vivo and endothelial antithrombotic function ex vivo (81). These findings have been supported in humans where impaired endothelium–dependent vasodilation has been related to increased levels of homocysteine (84). In cell culture systems a variety of deleterious effects on the endothelium and haemostasis has been shown. These effects include inhibition of the thrombomodulin–protein C pathway (85, 86), prostacyclin synthesis, impaired regulation of endothelium–derived relaxing factor (87), and blocking of tPA–binding to endothelial cells (88).
A major shortcoming of these observations is that most in vitro effects of homocysteine on endothelial cells have been demonstrated for homocysteine concentrations exceeding the levels encountered even under the most severe pathological conditions. Therefore their pathophysiological relevance awaits confirmation from in vivo studies.

### Cognition and cerebellum

The clinical features of brainstem (BI) and cerebellar infarcts (CI) and their relation to different vascular territories have been described in several studies involving elderly stroke patients (89), whereas detailed information on infratentorial infarcts in the young (18-45 years) have scarcely been reported (9, 90). Little information is thus available for this subgroup concerning clinical features, aetiology and prognosis.

![MRI of posterior fossa](image)

**FIGURE 8. MRI OF POSTERIOR FOSSA (T2-WEIGHTED IMAGE) IN A 38 YEAR OLD WOMAN WITH A RIGHT VERTEBRAL DISSECTION. A LARGE RIGHT CEREBELLAR HEMISPHERIC LESION MAINLY IN THE SUPERIOR CEREBELLAR ARTERY TERRITORY WITH INCREASED SIGNAL INTENSITY IS IDENTIFIED.**

The human cerebellum contains more neurons than the rest of the brain, and is connected with all major subdivisions of the central nervous system including the basal ganglia, diencephalon, limbic system, brainstem, cerebellum and spinal cord. Anatomical and physiological studies in animals indicate that the cerebrocerebellar circuit consists of afferent inputs through cortico–ponto–cerebellar pathways and a feedback limb through cerebello–thalamic–cortical pathways (91) (Figure 9). Besides
the sensorimotor cortices, the association areas of the frontal, temporal and parietal lobes and the paralimbic cortices are integrated parts of this system. These structures are involved in cognitive as well as motor functions.

FIGURE 9. DIAGRAM OF THE CEREBROCEREBELLAR CIRCUIT. Feedforward limb: The corticopontine pathway (A) carries associative, paralimbic, sensory, and motor information from the cerebral cortex to the neurons in the ventral pons. The axons of these pontine neurons reach the cerebellar cortex via the pontocerebellar pathway (B). Feedback limb: The cerebellar cortex is connected with the deep cerebellar nuclei (DCN, C), which project via the red nucleus to the thalamus, the cerebello-thalamic projection (D). The thalamic projection back to the cortex (E) completes the feedback circuit. With permission: Schmahmann JD et al. The cerebrocerebellar system. International Review of Neurobiology 1997;41;31-60.

The term cognition usually refers to thought processes such as executive function, learning, memory, visual analysis, and language. Cognitive deficits in stroke patients can occur both in multiple domains or can be highly selective.

During the early years of neuropsychology, the emphasis was on the relationship between localized injury to the brain and specific behavioural symptoms. Today, with modern imaging techniques such as magnetic resonance imaging widely available, the emphasis is no longer on the localising value of specific cognitive symptoms but rather on the identification and quantification of degree and pattern of specific cognitive and motor impairment. The idea that complex cognitive skills are carried out by distinct subprocesses combined with the idea that there are highly specialized areas in the brain, has led to the assumption that a cerebral lesion can damage only some subprocesses within complex cognitive skills. The modularity approach to the analysis of cognitive skills implies that each complex cognitive process can be thought of as consisting of a series of functionally independent specialized subprocesses. The interaction of these processes results in complex cognitive skills. The way in which the cognitive processes are organized can be characterised in terms of flow diagrams that attempt to detail the way that the different subprocesses are brought together to perform a specific task. A neuropsychological assessment allows the
<table>
<thead>
<tr>
<th>Domain</th>
<th>Tests</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>General intellectual abilities</td>
<td>Wechsler Adult intelligence Scale-Revised (WAIS-R)</td>
<td>Detailed assessment of both verbal and nonverbal aspects of cognitive performance; provides separate verbal and nonverbal performance IQ scores</td>
</tr>
<tr>
<td>Attention</td>
<td>Digit span (forward/backward)</td>
<td>Measure of verbal attention span (subtest of WAIS-R)</td>
</tr>
<tr>
<td>Language</td>
<td>Boston Naming Test</td>
<td>Visual confrontation naming, line drawing</td>
</tr>
<tr>
<td></td>
<td>Writing to Description</td>
<td>Subtest of Boston Diagnostic Aphasia exam; assess ability to provide written description of a picture</td>
</tr>
<tr>
<td></td>
<td>Repetition</td>
<td>Subtest of Boston Diagnostic Aphasia exam; repetition of words and sentences</td>
</tr>
<tr>
<td>Memory</td>
<td>Wechsler Memory Scale-revised (WMS-R)</td>
<td>A memory test battery with subtest that assess orientation, attention, verbal and visual memory</td>
</tr>
<tr>
<td>Visuo-Construction</td>
<td>Block Design (WAIS-R)</td>
<td>A test requiring the patient to assemble 3-dimensional blocks to match a 2-dimensional design</td>
</tr>
<tr>
<td>Visuo-Perceptual</td>
<td>Picture completion (WAIS-R)</td>
<td>Requires identification of missing details from line drawings</td>
</tr>
<tr>
<td>Abstraction/Problem solving</td>
<td>Wisconsin Card Sorting Test</td>
<td>A test of problem and abstraction requiring the patient to infer decision-making rules from feedback given during the test</td>
</tr>
<tr>
<td></td>
<td>Similarities (WAIS-R)</td>
<td>A test of verbal abstraction requiring the patient to state what two concepts have in common</td>
</tr>
<tr>
<td></td>
<td>Verbal Fluency</td>
<td>A verbal test requiring the patient to generate as many words as possible that start with a certain letter in a 60 second period</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>Trailmaking Test</td>
<td>A test of psychomotor speed and mental flexibility. Trail A requires the patient to connect numbered circles in sequence as quickly as possible. Trail B requires connecting alternating numbers and letters in sequence as quickly as possible</td>
</tr>
</tbody>
</table>

TABLE 6. COGNITIVE DOMAINS AND RELEVANT TESTS
description and evaluation of the major cognitive deficits incurred in patients with brain damage, e.g., stroke. The assessment of general intellectual abilities is an important part of the neuropsychological examination, because performance on most neuropsychological tests is highly correlated with intelligence quotient (IQ). The most frequently used measure of general IQ is the WAIS–R (92). The main cognitive domains evaluated during a neuropsychological examination are listed in Table 6; representative tests for each domain are included.

FIGURE 10. A SIMPLIFIED REPRESENTATION OF THE WORKING MEMORY MODEL. Working memory is defined as the formation of temporary representations of important events, contexts and recalled experiences that are used to support other mental functions (115). It has been proposed that working memory includes a central executive system to control attention and information flow to and from verbal (the Articulatory loop) and spatial (the Visuo-spatial sketch pad) short term memory buffers ("slave systems"). Adapted from: Baddeley A. Working Memory. Oxford University Press, 1986.

Over the years, evidence has emerged which supports the theory that the cerebellum is involved in diverse cognitive neurobehavioral systems. Support for this view derives from lesion studies, anatomic and neuroimaging studies (93–94). However, the specific anatomical basis of cognitive processing in the cerebellum is poorly understood. Investigations have comprised functional imaging studies of healthy individuals (91, 95) and clinical observations and neuropsychological testing in patients with neurodegenerative diseases (20, 96). However, since many of these diseases are multifocal rather than confined to the cerebellum, the exact contribution of cerebellar damage to cognitive impairment and clinical deficits remains unclear. Functional neuroimaging studies of the cerebellum involving normal subjects point to
cerebellar activation in a variety of nonmotor functions, including sensory discrimination (97), working memory (98), attention (99), verbal learning and memory (100), and cognitive flexibility (101). In functional neuroimaging studies, cerebellar activation has been shown to correlate with demanding verbal tasks, presumably loading high upon central, executive aspects of working memory and recently a specific lobular pattern of cerebellar activation during verbal working memory was reported (102).

In neuropsychology, the concept of working memory is increasingly attracting interest (Figure 10). The working memory system is challenged, particularly when subjects are asked to perform novel tasks, difficult tasks, or to do several things at the same time. The concept of working memory subsumes somewhat outdated concepts, such as short-term memory, primary memory and immediate memory. In contrast to the latter concepts, which emphasize temporary storage of information, the literature on working memory seeks to clarify how storage and processing of information influence concurrent mental activity. The emphasis on the use of information held in temporary storage seems, at least at the outset, to have a bearing on problems that often are reported by patients who have suffered from brain damage. Such problems include fatigue, absent-mindedness and forgetfulness. By a similar token, the families, friends, and work mates of the patients sometimes make remarks regarding planning abilities, forgetting, and carelessness. These symptoms suggest the involvement of the central executive processes, rather than the other components of the working memory model. Hence, neuropsychological investigations dealing with the more complex constituents of working memory may provide information about cognitive problems that may go unnoticed in routine assessment.
Objectives

1. To study the fundamental pathophysiological changes and long-term outcome in cerebrospinal fluid hydrodynamics in young patients with superior sagittal sinus thrombosis over time.

2. To evaluate age-specific incidence of ischaemic stroke in young adults in northern Sweden.

3. To establish an accurate hierarchy of causes of ischaemic stroke in young adults.

4. To study plasma fibrinogen levels and specific components of the fibrinolytic system, and these factors possible interrelationship with other vascular risk factors.

5. To study possible abnormalities in total plasma homocysteine, measured both in the fasting state and after methionine loading.

6. To assess whether the C677T mutation in the methylenetetrahydrofolate reductase gene was associated with increased risk of ischaemic stroke.

7. To study possible associations between plasma total homocysteine levels and fibrinolytic factors.

8. To evaluate cognitive functions and outcome for young patients with isolated infratentorial infarcts.
Patients

Paper I

Between 1975 and 1990, 13 patients admitted to the Department of Neurology, University of Umeå, had a selective cerebral angiography verified diagnosis of non-septic SSST. All patients had at least one CT scan with contrast enhancement and 8 had two or more examinations. Ten of the patients (7 women and 3 men) were followed over a mean of 5.8 years (range 2–15 years) with repeated CSF hydrodynamic investigations.

Paper II–V

Patients included in paper II–V are described in Figure 11.

Paper II

EPIDEMIOLOGICAL PART

Acute stroke events in the two northernmost counties have been monitored since 1985 by the WHO Northern Sweden MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) project (103). The case finding and validation of data quality has been described in detail earlier (104).

Clinical information from discharge records on all subjects in the age range 18 to 45 years with International Classification of Diseases (ICD-9) codes 430–438 was screened and validated for acute stroke events which met the definition of ischaemic stroke. This part of the study thus contains patients referred to Umeå university hospital (included in the aetiological study – see below) and patients only investigated at local acute-care hospitals in Northern Sweden (Figure 11). The same inclusion and exclusion criteria as in the aetiological study were used.
STROKE IN YOUNG ADULTS

STUDY POPULATION

Patients fulfilling the criteria for ischemic stroke

Evaluated at Umeå university hospital

Diagnosed and evaluated at secondary care hospitals in the MONICA area

Patients fulfilling the criteria for ischemic stroke

Living in the MONICA area

The MONICA area

AETIOLOGICAL PART

One hundred-seven patients aged 18–44 years with a first ever ischaemic stroke admitted to Umeå University Hospital were included. The inclusion criteria were as follow: (1) first ever completed ischaemic stroke defined as a rapidly developing focal neurological deficit with no apparent cause other than a vascular origin, that persisted
beyond 24 hours in surviving patients; (2) age from 18 through 44 years; (3) evaluation possible within 3 months following stroke onset. Exclusion criteria were: ischaemic stroke due to complications of subarachnoid haemorrhage, cardiac surgery, malignancy in a terminal stage or occurring as an immediate consequence of trauma. Patients were scheduled for follow-up at four and twelve months after admission.

Paper III

Fibrinolytic studies were undertaken in 102 patients (3 patients died in the acute phase of the disease and 2 patients were lost to follow-up) at a follow-up visit at least 3 (mean 5.4 ± 2.0) months after admission. At the time of blood sampling 12 patients were on treatment with oral anticoagulants. Ninety patients received a low dose of aspirin as secondary prophylaxis.

Paper IV

Of the 107 patients originally included, 86 patients were consecutively enrolled from the beginning of 1992 to May 1996 when the method for analysis of plasma tHcy was available for routine use. In eighty patients investigations of the homocysteine metabolism were undertaken at least 3 (mean 5.1 ± 1.9) months after admission. In three patients this particular investigation was not carried out. Two exclusions were due to early death and one patient was not available for follow up.

Paper V

Twenty-four patients (12 men and 12 women; 36.9 ± 6.5 years) with isolated cerebellar or brain stem infarcts were identified during the study period.
Controls

Paper I

The normal values for CSF hydrodynamic variables were obtained in patients in whom medical history, as well as medical and neurological investigation, indicated no organic neurological or circulatory disorder (105).

Paper III and IV

Forty-one healthy control subjects were recruited by local announcement from the University faculty and staff and from the Umeå community at large. The healthy controls had no history of hypertension, diabetes mellitus, hyperlipidemia, malignancy, vascular disease or any other major disease that might affect the vascular endothelium.

Paper V

The control group consisted of 14 healthy volunteers (nine male and five female) recruited by local announcement.
Methods

Paper I

CSF HYDRODYNAMIC INVESTIGATION

The CSF hydrodynamic investigation was performed according to the constant pressure infusion method described by Ekstedt (106) (Figure 12).

CSF resting pressure (Pci) was determined when the resting recording had been stable for at least 10 min., which usually required 30–60 min. recording. The conductance of the CSF outflow pathways (Gop) was determined by applying multiple pressure levels to the CSF space while recording the resulting inflow of CSF.
artificial CSF. The volume accounting method was used to calculate the pressure/flow relationship. The slope for the pressure/flow values is equal to the CSF outflow conductance (Figure 13).

![Figure 13. The relationship between flow of artificial CSF (q) and CSF pressure (p) into a patient.](image)

The CSF formation rate (qf) was determined by lowering the CSF pressure to a value of about 0 kPa for a sufficient period to produce a stable pressure and outflow into the bottle.

Finally, the pressure difference across the CSF outflow pathways (Pdop) and the sagittal sinus pressure (Pss) were calculated according to the formula (10):

\[ P_{dop} = \frac{qf}{G_{op}} \text{ and } P_{ss} = P_{cl} - P_{dop} \]

The calculated values of Pss express the mean value of the pressures in the major dural sinuses.

Paper II–V

**CLASSIFICATION OF STROKE SUBTYPES**

The patients were classified independently by two groups of paired investigators. A consensus approach was applied when necessary. The main diagnostic criteria are presented in Figure 15 (see Result section).

**CLINICAL INVESTIGATION**

Medical history and information regarding cerebrovascular risk factors such as arterial hypertension, diabetes mellitus, smoking, alcohol use, illicit drug use, hyperlipidemia, oral contraceptive use, history of migraine and occurrence of venous or arterial thrombosis in the family were obtained according to a standardised protocol.
NEUROIMAGING

Neuroimaging included CT and 0.5 T superconducting MRI of the brain at onset of symptoms. Patients without lesions on the initial CT scan were reexamined during the acute phase with a second CT scan and/or a MRI. Selective angiography of both carotids and at least one vertebral artery was performed, and in selected cases magnetic resonance angiography. In paper V, the anatomical location and the largest diameter of the infarct area were selected (107–109) from consecutive neuroradiological investigations performed within the two–month period following the stroke.

TRANSTHORACIC AND TRANSESOPHAGEAL ECHOCARDIOGRAPHY

All examinations were recorded on videotape and analysed blinded off-line in a random order. Atrial septum aneurysm (ASA) was diagnosed when the atrial septum appeared abnormally redundant and mobile and exhibited an excursion into the left or right atrium, or both, of > 10 mm and a base width of 10 mm. For patent foramen ovale (PFO), the echocardiographic detection of interatrial right–to–left shunting was identified by colour–flow Doppler or by the administration of 5 mL agitated saline in an antecubital vein. Two to four contrast injections were systematically performed in each patient, both in the resting state and during provocative maneuvers (Valsalva and cough test) to transiently reverse the interatrial pressure gradient. The echocardiographic diagnosis of PFO was based on the appearance of at least three microcavitations, either spontaneously or after provocation maneuvers, into the left atrium, not later than four cycles after the appearance of the microcavitations in the right atrium. The presence of atherosclerotic plaques of any severity was noted when detected on echocardiography, occurring between the aortic valve and the origin of the left subclavian artery. Mitral valve prolapse was defined on TTE as mitral leaflet thickening and displacement beyond the plane of the mitral annulus and into the left atrium in the parasternal long–axis view during systole.

OTHER INVESTIGATIONS

Duplex ultrasonography of the cervical arteries, electrocardiography and 24–hour electrocardiography Holter recording were performed.

LABORATORY INVESTIGATIONS

Besides routine laboratory tests, the following tests were also performed: antinuclear (ANA) and anticardiolipin antibodies of the IgG isotype (IgG aCLs), rheumatoid factor, complement factors (C3/C4), serological testing for syphilis, borreliosis and viral infections (including HIV), serum cholesterol and triglyceride levels, low and high density lipoprotein levels, lipoprotein(a), prothrombin and activated partial thromboplastin times (aPTT). aPTT was also used as a screening test for the presence of lupus anticoagulants. Levels of protein C, protein S and antithrombin III were analysed both in the acute phase and at least three months after first admission.
ANALYSIS OF FIBRINOLYTIC ACTIVITY (PAPER III-IV)

Sampling took place in the early morning (7.00-9.00 a.m.) after an overnight fasting. Venous blood samples were drawn from the antecubital vein without stasis after 10 minutes of bed rest into evacuated glass tubes (Venoject) containing 1/100 volume of 0.5 mol/L EDTA, or, for the fibrinolytic assays (110), into 1/10 volume of 0.45 mol/L of citrate, pH 4.4 (Stabilyte® tubes, Biopool, Umeå, Sweden).

A venous occlusion test (Paper III) was performed on the opposite arm by inflating a blood pressure cuff to 100 mmHg for 10 minutes. Blood was then collected in another Stabilyte tube for measurement of tPA activity and tPA mass concentration after venous occlusion. Plasma and serum aliquots were prepared by centrifugation at 1500g for 15 minutes at room temperature and stored within 1 hour at −80°C until assayed. Plasma samples that were thawed only once were used.

Plasma levels of each haemostatic factor were determined using the following assay systems: the mass concentration of tPA in plasma (in former studies often termed "tPA antigen") was determined with an enzyme-linked immunosorbent assay (Imulyse® tPA) obtained from Biopool, Umeå, Sweden (111). The activities of tPA and PAI-1 were measured with chromogenic substrate assay based on the fibrin-stimulated tPA-mediated plasminogen to plasmin conversion (112). The reagent (Spectrolyse® Fibrin) was purchased from Biopool, Umeå, Sweden.

HOMOCYSTEINE ANALYSIS (PAPER IV)

Plasma tHcy concentrations were determined in EDTA-plasma by High Pressure Liquid Chromatography (HPLC) using electrochemical detection. In the concentration range of 10–50 μmol/L the inter assay coefficients of variation was 3.6 %. The samples of the controls were analysed at the same time. The samples of the patients were analysed during 1992–1996. However, reanalysis in 1997 of representative samples kept frozen yielded no significant differences.

After withdrawal of blood in the fasting state patients and controls received a single dose of 100mg/kg of L-methionine per os together with a standardised low-methionine breakfast. A second blood sample was taken 4 h after the methionine load. During the 4 h period, the patients were only allowed to ingest food poor in protein and methionine.

Plasma and serum aliquots were prepared by centrifugation at 1500g for 15 minutes at room temperature and stored within 1 hour at −80°C until assayed.

Assays of pyridoxal-5’-phosphate were performed by MIMELAB-AB in Söråker, Sweden by enzymatic photometry with HPLC separation.

GENOTYPING (PAPER IV)

DNA was extracted according to Caddy et al (113) after cell lysis, deproteinization with perchlorate and extraction with chloroform and resin, using the Nucleon DNA extraction kit from Nucleon biosciences, Coatbridge (UK). The extracted DNA was stored at −80°C until analysis. The DNA samples were subjected to amplification by the polymerase chain reaction and the restriction enzyme HinfI was used to identify those with the C677T mutation. The mutant allele was designated as "T" and the wild-type as "C".
The median time from stroke onset to the neuropsychological evaluation was 16 days. All the neuropsychological tests in both patients and controls were done by the same neuropsychologist. The tasks were administered on two consecutive days (part 1 and part 2). During the first session (part 1) a battery of well-known and established neuropsychological measures was used (Table 6). The second session (part 2) assessed episodic memory, (i.e., the recollection of specific past events), and working memory (Table 7).

**Short term memory.** The system which stores a limited amount of information for a short period of time; if the information is not refreshed continuously, it decays in a matter of seconds.

**Working memory.** A broader concept of short term memory and refers to a system for temporary storage and manipulation of information, a function critical for a wide range of cognitive operations. Current models of working memory emphasise separate subsystems for handling verbal and spatial information. These separate subsystems are under the directive of a central executive system which directs attention and organises information from different modalities (see also figure 10).

**Long term memory.** The system which stores an unlimited amounts of memoranda for a variable period of time (from minutes to years). It includes the following:

- **Declarative or explicit memory.** Memory which is consciously accessed, comprising:
  - **Episodic memory,** personal experienced facts and events, with specific spatial and temporal localization, including e.g. all autobiographical information.
  - **Semantic memory,** culturally and educationally aquired encyclopaedic knowledge e.g. meaning of words, arithmetical facts and geographical and historical information.

- **Implicit or procedural memory.** Retains information that affects behaviour but is not available for conscious recollection e.g. motor skills, conditioned reflexes, priming.

**TABLE 7. CLASSIFICATION OF MEMORY.**

Episodic memory was evaluated by means of immediate free recall of lists of words. Four lists of words were read to the subjects. Following each list, the subjects were asked to recall as many words as possible. Two of the lists were read to the subjects at a rate of one word every five seconds. Two other lists were read at a pace of one word every two seconds. Ninety seconds were allowed for free recall. Two measures were derived from the recall protocols. The recency items, i.e., the three last items in each list, were removed from the analysis of episodic memory. Hence, episodic memory performance was based upon the recall of pre-recency items.

Attention and working memory were addressed using Daneman and Carpenter’s sentence span task (114), the digit span task of the WAIS–R, and a word span task, where words were presented for immediate serial recall. The working memory span task was used to tap complex attention, the digit span task was used to monitor less effortful attentional skills and the word span task was assumed to reflect an intermediate level of attentional demands (115).
At follow up, the modified Rankin scale (116) and the NIH stroke scale (117–118) were used for assessment of disability and neurological dysfunction, respectively. Working capacity (after optimal adjustments) was assessed in relation to prior occupation and according to the guidelines of the Swedish social insurance scheme (www.fk.se). Patients were scaled as 0% or 50% of prior maximal working capacity if they drew sickness allowance. Otherwise they were scaled as 100%.
Results

Paper I

CLINICAL OUTCOME AND NEUROIMAGING
Mean age was 29.1 ± 11.4 years. Six patients had a well-defined syndrome with symptoms related to intracranial hypertension (headache, papilloedema, impaired consciousness), with or without generalized epileptic seizures. The others had focal symptoms, with or without signs of intracranial hypertension. Two patients were left with sequelae. Only one of the 4 patients who had generalized epileptic seizures in the acute phase had later recurrence. There was no recurrence of cerebral venous thrombosis during follow-up.

Selective carotid angiography identified 7 patients with an isolated SSST. The occluded sinus could not be visualized in 5 patients, indicating complete thrombotic occlusion. The three patients investigated at least one month after onset all had a partial, isolated thrombosis. In all but one patient collaterals were visualized.

CSF HYDRODYNAMIC VARIABLES
CSF hydrodynamic variables are shown for two of the patients in Figure 14. All patients had raised sagittal sinus (Pss) and intracranial pressure (Pci) at their first investigation. The pressure difference across the CSF outflow pathways (Pdop) was a preserved or slightly increased. Pressure levels (Pss and Pci) gradually declined over time in all patients but only returned to normal in two patient after 8 and 15 years, respectively. The presence of total or partial thrombotic occlusion on initial angiography did not appear to correlate with the long-term development of pressure levels.

Conductance was normal or slightly to moderately decreased. A more pronounced decrease was seen in patients with a complete sagittal sinus thrombotic occlusion. No consistent changes in conductance were seen although in some cases an initial decreased conductance was later normalized. CSF formation rate (qf), which was normal in all patients, did not vary over time.
FIGURE 14. COURSE OF VARIOUS PRESSURES ($P_{cl}$, $P_{ss}$, $P_{dop}$) AND CONDUCTANCE ($G_{op}$) PLOTTED AGAINST TIME IN TWO PATIENTS. DOTTED LINE IN PRESSURE VALUE CURVES MARKS 90% CONFIDENCE INTERVALS LIMIT FOR $P_{cl}$ UPPER VALUE. LOW CONDUCTANCE VALUES ARE DEFINED AS VALUES FALLING WITHIN SHADED AREA ON $G_{op}$ CURVES.

Paper II

EPIDEMIOLOGICAL DATA

A total of 88 first ever ischaemic strokes in the age range 18 through 44 years from the MONICA surveillance area were recognized during the study time. Seventy-one cases (81%) were primarily evaluated or referred from secondary level care-settings for further investigations at the University Hospital. These patients are thus included in the aetiological study part. The additional 17 cases, all admitted to local acute-care hospitals, were identified from the MONICA project register.

The average annual incidence rate of first ever ischaemic stroke in the age group 18–44 years was 11.3/100 000. Ischaemic stroke in young adults thus represented 3.9% of all ischaemic strokes in the age group 18–74 years. Five patients died within 28 days, resulting in a case fatality rate of 5.7%.

AETIOLOGY OF ISCHAEMIC STROKE (PAPER II–V)

Sixty-three males and 44 females (36.5 ± 6.2 years (range 19–44 years)) fulfilled the inclusion criteria. Selective angiography of both carotids and at least one vertebral
artery was performed in 95 patients (89%) and abnormalities related to clinical symptoms were found in 58 patients (61%). In addition three patients underwent MRI angiography. All patients were investigated by CT and 80 patients (75%) by MRI of the brain. Six patients did not display any visible ischaemic lesion on neuroimaging. One hundred and five patients (98%) underwent either a transthoracic or transesophageal echocardiographic investigation.

After completion of the aetiological workup, assessment of a probable or possible aetiology led to classification of the patients into one or more of eight diagnostic groups subdivided into higher priority (I–IV) and lower priority (V–VIII) diagnoses (Figure 15).

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Probable</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Atherothrombotic vasculopathy (11%)</td>
<td>* stenosis &gt; 60% or, * ulcerated plaque (plaque with intraluminal clot)</td>
<td>* any detectable atherosclerotic disease</td>
</tr>
<tr>
<td>II. Non-atherothrombotic vasculopathy (19%)</td>
<td>* angiographic evidence or, * clinical evidence and non-invasive testing positive</td>
<td>* clinical evidence/or diagnostic tests equivocal</td>
</tr>
<tr>
<td>III. Cardiac/transcardiac embolism (33%)</td>
<td>* major cardiac source</td>
<td>* minor cardiac source</td>
</tr>
<tr>
<td>IV. Hematological causes (7%)</td>
<td>(i.e., thrombocytopenia, deficiency of coagulation inhibitors, postpartum, autoimmune disease including APLA)</td>
<td>n = 8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Probable</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>V. Lacunar infarction (5%)</td>
<td>(one of the following: 1. infarct &lt; 15 mm in the territory of the deep perforators compatible with deficit and lacunar syndrome; 2. lacunar syndrome (except sensorimotor stroke) and normal imaging)</td>
<td>n = 5</td>
</tr>
<tr>
<td>VI. Migraine induced stroke (1%)</td>
<td>(according to the IHS criteria (Cephalgia 1988;8(suppl 7):1-96))</td>
<td>n = 1</td>
</tr>
<tr>
<td>VII. Oral contraceptives (3%)</td>
<td>(current use)</td>
<td>n = 3</td>
</tr>
<tr>
<td>VIII. Indeterminate causes (21%)</td>
<td>(when no other diagnoses are satisfied)</td>
<td>n = 22</td>
</tr>
</tbody>
</table>

FIGURE 15. CAUSES OF ISCHAEMIC STROKE IN YOUNG PATIENTS EVALUATED AT UMEÅ UNIVERSITY HOSPITAL. Abbreviations: IHS, International Headache Society; APLA, antiphospholipid antibodies.

The distribution of the main diagnostic categories for the patients evaluated in paper III (n = 102), paper IV (n = 80) and paper V (n = 24) are shown in Table 8.
Table 8. Causes of Ischaemic Stroke in Paper III-V. Number of patients (percent).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Paper III (n = 102)</th>
<th>Paper IV (n = 80)</th>
<th>Paper V (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic vasculopathy</td>
<td>13 (13)</td>
<td>10 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Cardioembolic causes</td>
<td>34 (33)</td>
<td>29 (36)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Non-atherosclerotic vasculopathy</td>
<td>18 (17)</td>
<td>18 (22)</td>
<td>8 (33)</td>
</tr>
<tr>
<td>Haematologic disorder</td>
<td>6 (6)</td>
<td>3 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Lacunar infarct</td>
<td>4 (4)</td>
<td>4 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Migraineous stroke</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>3 (3)</td>
<td>3 (4)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>22 (22)</td>
<td>13 (16)</td>
<td>7 (29)</td>
</tr>
</tbody>
</table>

Table 9. Distribution of Fibrinolytic Variables and Fibrinogen in Patients and Controls. Median and Interquartile Range (IQ). Abbreviations: PAI, plasminogen activator inhibitor; tPA, tissue plasminogen activator; VO, venous occlusion; P-value, Mann-Whitney U test.

**Fibrinolytic Variables**

In the baseline samples, patients had significantly higher fibrinogen levels, lowered tPA activity and increased PAI-1 activity, as well as increased tPA mass concentrations (Table 9). After venous occlusion (VO), the patients had higher mean levels of tPA activity and tPA mass concentration. In post-occlusion samples, only the difference in tPA mass concentration reached statistical significance. The diagnostic
subgroups did not differ significantly from each other except for tPA mass concentration after VO, which was significantly higher in the three diagnostic subgroups with documented vasculopathies or a cardioembolic source.

FIBRINOLYTIC VARIABLES IN RELATION TO OTHER VASCULAR RISK FACTORS

There were strong correlations between baseline fibrinolytic variables on one hand body mass index (BMI), serum triglycerides and cholesterol levels on the other hand. Baseline levels of tPA activity, PAI-1 activity, and plasminogen adjusted for BMI, serum triglycerides and cholesterol levels did not differ between groups, whereas fibrinogen levels and tPA mass concentrations both at baseline and after venous occlusion remained significantly higher among patients.

To assess the relative importance of possible explanatory variables for ischaemic stroke, a logistic regression analysis was applied. The analysis indicated that plasma fibrinogen was most strongly associated with the presence of ischaemic stroke followed by serum cholesterol, whereas tPA mass concentration barely failed to reach significance (Table 10).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>Std. Error</th>
<th>p</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol, mmol/L</td>
<td>2.58</td>
<td>0.76</td>
<td>0.001</td>
<td>1.44-4.61</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>7.97</td>
<td>4.02</td>
<td>&lt;0.001</td>
<td>2.96-21.4</td>
</tr>
<tr>
<td>Baseline tPA mass concentration, μg/L</td>
<td>1.15</td>
<td>0.08</td>
<td>0.059</td>
<td>0.995-1.32</td>
</tr>
</tbody>
</table>

TABLE 10. LOGISTIC REGRESSION ANALYSIS FOR ISCHAEMIC STROKE IN YOUNG ADULTS.
Abbreviations: CI, confidence interval.

Paper IV

HOMOCYSTEINE LEVELS

There was no difference in fasting and post-load tHcy levels between patients and controls. However, the increase after loading (i.e., post-load minus fasting level tHcy) was significantly higher among patients.

Table 11 shows the number of patients and controls with elevated tHcy levels. Of the 30 patients with elevated post-load increase of tHcy, 7 were also defined as having elevated fasting tHcy. Four patients had isolated fasting homocysteinemia. Hence, the overall prevalence of homocysteinemia in this patient population was 34% (27/80).
The diagnostic subgroups did not differ significantly from each other with respect to either fasting or post-load levels of tHcy (data not shown).

There was no difference between patients and control subjects in either (TT) genotype frequency or (T) allele frequency.

<table>
<thead>
<tr>
<th></th>
<th>Fasting levels</th>
<th>Post-load levels</th>
<th>Increase after load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated tHcy</td>
<td>≥ 15.3 µmol/L</td>
<td>≥ 39.9 µmol/L</td>
<td>≥ 24.6 µmol/L</td>
</tr>
<tr>
<td>Cases / controls (n)</td>
<td>11 / 4</td>
<td>13 / 4</td>
<td>30 / 4</td>
</tr>
<tr>
<td>Cases / controls (%)</td>
<td>13.8 / 9.8 (p = 0.5)</td>
<td>16.3 / 9.8 (p = 0.03)</td>
<td>37.5 / 9.8 (p = &lt;0.001)</td>
</tr>
<tr>
<td>Age - gender- adjusted</td>
<td>1.5 (0.4 - 4.6)</td>
<td>3.4 (1.1-10.8)</td>
<td>5.9 (1.9-18.3)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate adjusted</td>
<td>0.99 (0.1-4.0)#</td>
<td>2.7 (0.8-9.7)*</td>
<td>4.8 (1.4-16.7)‡</td>
</tr>
</tbody>
</table>

**TABLE 11. HOMOCYSTEINE LEVELS AND RISK OF ISCHEMIC STROKE.** The cutoff point for hyperhomocysteinemia was set at the 90th percentile of the homocysteine distribution in the healthy controls.

# adjusted for age, gender, BMI, triglycerides and smoking; * adjusted for age, gender, BMI, triglycerides and cholesterol; ‡ adjusted for age, gender, BMI, triglycerides, cholesterol and fibrinogen.

**ASSOCIATIONS WITH CEREBROVASCULAR RISK FACTORS**

BMI and triglycerides were significantly correlated with both fasting and post-load tHcy increase, whereas total and LDL cholesterol and fibrinogen were significantly correlated only with post-load tHcy increase.

Fasting tHcy levels were higher among smokers (p = 0.004) whereas the post-load tHcy increase did not differ between smokers and non-smokers (p = 0.2).

**PLASMA tHCY AND RISK OF ISCHAEMIC STROKE**

Odds ratios of ischaemic stroke for subjects with elevated tHcy relative to subjects with levels at or below the cutoff-points are given in Table 11. Elevated post-load increases of tHcy levels were associated with a 5.9-fold increased risk of ischaemic stroke after adjustment for age and gender. After adjustment for possible confounding factors, the odds ratio for elevated post-load increase levels remained significant with a 4.8-fold increased risk of ischaemic stroke.

**HOMOCYSTEINE AND FIBRINOLYSIS**

There were significant correlations between post-load increase in tHcy levels and the fibrinolytic variables across the whole group.

In the entire study population an abnormal increase in post-load tHcy levels
 (> 90th percentile) was associated with higher plasminogen, tPA mass concentration and PAI-1 levels and lower tPA-activity (Table 12). After adjustment for age, sex, BMI, serum cholesterol and triglycerides an abnormal increase in post-load tHcy levels remained significantly associated with plasminogen (p = 0.001) and tPA mass concentration levels (p = 0.03).

There was no increase in vWF levels among subjects with an abnormal post-load tHcy increase.

<table>
<thead>
<tr>
<th>Increase after load &lt; 90th percentile</th>
<th>Increase after load &gt; 90th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>IQ range</td>
</tr>
<tr>
<td>Plasminogen</td>
<td>1.7</td>
</tr>
<tr>
<td>tPA activity</td>
<td>0.1</td>
</tr>
<tr>
<td>tPA mass concentration</td>
<td>6.8</td>
</tr>
<tr>
<td>PAI-1 activity</td>
<td>8.6</td>
</tr>
</tbody>
</table>

TABLE 12. FIBRINOLYTIC VARIABLES AMONG SUBJECTS WITH NORMAL INCREASE IN tHCY AFTER METHIONINE LOAD (< 90TH PERCENTILE OF THE CONTROL GROUP). Abbreviations: IQ, interquartile range (25 and 75 percentiles); tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor.

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**Paper V**

**INFRATENTORIAL INFARCTION**

Eighteen patients had a neuroradiologically verified infarct in one (7 left-sided and 6 right-sided) or both cerebellar hemispheres (5 patients). MRI was normal despite repeated investigations in two of the 24 patients, both with a clinical picture well in agreement with an infratentorial infarction. Four patients had brainstem infarcts: two had lateral medullary infarcts without involvement of the cerebellum and two had isolated pontine infarcts. A potential cause of the infarct was found in 17 patients (see Table 8).

**OUTCOME**

Twenty-two (92%) of the patients had a favourable outcome at the four and twelve months follow-ups according to the modified Rankin scale (grade 0–2). Only two patients developed major neurological sequele according to the NIH stroke scale. However, 12 (52%) of the patients were granted sick-leave four months after the onset despite optimal working adjustments. The corresponding figure at the twelve-month follow-up was 10 (43%). The majority of patients had complaints of
neuropsychiatric symptoms such as memory loss, irritation, agitation, anxiety and fatigue. No major depression was observed clinically. The maximal working capacity and modified Rankin scale at the four- and twelve-month follow-ups were closely associated with the maximal diameter of the lesion in patients with cerebellar infarcts.

**COGNITIVE FUNCTION**

Twenty of the 24 patients participated in at least one of the two neuropsychological sessions during the initial investigation and 15 patients participated in both.

There were highly significant differences between groups with respect to the Digit Symbol Task ($F(1.20)=42.72, P<0.001$) and the Trail-Making A task ($F(1.20)=20.85, P<0.001$). The results from the three span tasks were analysed by means of three separate a priori F tests. A statistically significant effect of Group (patients versus controls) was obtained for the working memory span task; $F(1.25)=8.45, P<0.01$ (Figure 16).

![Figure 16. Results pertaining to working memory for controls and patients.](image)

Significant negative correlations were seen between verbal and performance IQ versus the size of the cerebellar lesion ($r=-0.74$ and $-0.78$, respectively).

Furthermore, the relation between the block design task and maximal working capacity was analysed by means of two one-way ANOVAs. The patients were divided into three groups on the basis of their maximal working capacity (above). At four months, there was no statistically significant difference between the three groups, whereas at twelve months the difference was statistically significant ($F(2.11)=5.69; MSE = 35.56; p < 0.025$).

The correlation between the block design task and the modified Rankin scale of outcome was assessed by means of Spearman's rank order correlation. The results of these analyses indicated a correlation of moderate strength between outcome of the block design task during the first hospital stay and the modified Rankin scale at four months ($r_s = -0.47$) and at twelve months ($r_s = -0.46$).
Discussion

Cerebral venous thrombosis

This is the first long term study of cerebrospinal fluid hydrodynamics in patients with superior sagittal sinus thrombosis (SSST). In accordance with the literature the patients were young with a female predominance. None of our patients underwent shunting or other neurosurgical procedures and only two patients were optimally treated with anticoagulants (heparin in the acute phase). Some patients had a short term medical treatment aimed at reducing brain edema in the acute phase. Our patients may thus reflect the natural course of the condition.

Despite that neither acute cases with a fulminant course nor the benign forms which recovered rapidly and completely are likely to have been referred, the clinical characteristics of our patient group do not, however, essentially differ from contemporary clinical material (24). The latter manifestations have probably escaped detection in the era before the advent of MRI, a technique not available during the study period.

PRESSURE DYNAMICS

There are three intracranial compartments, i.e., brain tissue, blood and CSF, that can cause intracranial hypertension if pathologically altered. Our view of the predictable hydrodynamic consequences of a superior sagittal sinus thrombosis is illustrated in Figure 17.

In our patients, the main hydrodynamic features were increase of sagittal sinus pressure (Pss) and CSF resting pressure (Pcl). When sagittal sinus pressure is raised, engorgement of cortical veins is likely to cause an increase in total intracranial blood volume due to the impaired venous flow into the sagittal sinus. This excess intracranial volume may further increase intracranial pressure. The increase of intracerebral venous blood pressure elevates hydrostatic capillary pressure, thereby producing an increase in net capillary filtration and the possibility of a progressive cerebral edema. Ventricular compression may be seen on CT scan in up to 50% of patients in the acute phase of SSST (123).
The increase in brain volume could in itself lead to an additional increase in Pss. Direct compression of the sinuses and lateral lacunae may follow elimination of the parasagittal subarachnoid space, further compromising venous outflow.

**COLLATERAL VENOUS CIRCULATION**

If further pressure elevation occurs or is not relieved, coma and death may ensue. In most patients, however, the deterioration is transient and spontaneous improvement is the rule. This improvement is probably more a reflection of the adequacy of collateral channels than to restoration of blood flow through a recanalised occluded sinus lumen (124). The persistently high Pss in our patients may well indicate that the thrombotic occlusion commonly is a permanent one. In patients who survived for a considerable period after SSST, but later succumbed and were autopsied, the lumen of the superior sagittal sinus has been reported to be almost completely occluded by fibrous tissue with only small sinusoidal channels present which would not have permitted adequate drainage of venous blood from the brain (124). In the individual
patient, the amount of blood flowing out through collaterals or a partially patent sinus probably varies. Collaterals were present in all our patients who had a complete thrombosis. A decrease in pressure levels over time may be related to the development of a more extensive collateral system.

**CSF OUTFLOW CONDUCTANCE**

An occlusion of the superior sagittal sinus may, to some degree, obstruct resorption of CSF by the arachnoidal villi, i.e., a lower conductance, leading to increased CSF pressure. In our patients, conductance was normal or only slightly to moderately decreased (moderate reduction occurring in patients with a complete thrombosis). Conductance, when failing to improve during follow up, could be a consequence of a permanent disturbance of arachnoidal villi function. As CSF formation rate did not vary, \( P_{dop} \) will be preserved, or increased when conductance is lowered according to the classic relationship \( P_{dop} = \frac{qf}{G_{op}} \). The maintenance of the cerebrospinal–sagittal sinus gradient encourages CSF resorption. Alternative CSF pathways through venous collateral vessels may also play a role in CSF drainage. Therefore, a fairly small disturbance occurs in the CSF absorption process with only a minor contribution to intracranial pressure elevation.

**THE LONG-TERM CSF HYDRODYNAMIC OUTCOME**

Hydrodynamic abnormalities, in particular raised CSF pressure mainly due to raised \( P_{ss} \), persists many years after SSST. A change in conductance or CSF resorption facility plays only a minor role in the increase of intracranial pressure. However, the limited ability to compensate for a possible additional increase in intracranial pressure may pose the patients with SSST at a higher risk for complications in the event of a new stroke or a head injury.

**IMPLICATIONS FOR TREATMENT**

Treatment in the acute phase should aim at induce thrombolysis and prevent further thrombosis. Effective thrombolysis in the early stage might prevent the persistent intracranial pressure elevation that we saw in our patient group. Several small series have reported the use of fibrinolytic therapy with varying success (125–127), but in most cases without severe complications.

Early heparin treatment has been suggested to improve outcome by preventing thrombus extension (128) which further compromises the outflow of venous blood, and additionally increases intracranial pressure. Despite some controversy, heparin treatment is regarded as the mainstay in the treatment of cerebral venous thrombosis, even in patients with intracranial haemorrhage, provided there is no general contraindication to the use of heparin (24, 129). Treatment with local thrombolysis is reserved for patients worsening despite symptomatic treatment and adequate heparin treatment.
**Epidemiology**

The crude incidence rates for ischaemic stroke in Northern Sweden are higher than those reported earlier from most countries in Western Europe (30, 130–133) (Table 3) and similar to those among whites in Baltimore, USA (4). One study from Israel has provided information from this decade with an estimated incidence for ischaemic stroke of 5/100 000 in the age group 17–44 years (134). Our rates are only lower when compared to the unusually high rates of stroke among males and females 15–40 years of age in Benghazi, Libya (135) and among blacks in Baltimore, USA (4). The reported 50% higher incidence rates for ischaemic stroke in the elderly population of the Northern Sweden MONICA study when compared to available data from the MONICA study of Gothenburg, Sweden (130) together with older limited data from the Stockholm region (131) may suggest a south to north "stroke gradient" in Sweden. The explanation for such a possible geographical variation is currently unclear.

In accord with other studies, incidence rates for both males and females were found to rise steeply after the age of 35 (136). In our study this increase was mainly explained by an increase in the number of arterial dissections and cardioembolic cases, but only to a minor degree by an increase in premature atherosclerosis. A case fatality rate of 5.7% in the present study is considerably lower, as expected, in comparison with elderly stroke patients but corresponds to case fatality rates reported for similar age groups in epidemiological studies (30, 130) and case series (16, 17).

**Aetiology**

The criteria for atherosclerotic disease have varied considerably. Several studies included cases defined only by the coexistence of risk factors for atherosclerosis which may explain why atherosclerosis has been considered to be the cause of stroke in 5–50% of patients below 50 years of age (7, 16). Using the TOAST classification, we detected 3.7% of patients with a probable atherosclerotic vasculopathy; when using similar criteria for probable atherosclerotic vasculopathy the rate of atherosclerotic aetiology in recent studies has varied between 5% to 23% (12, 13, 16, 17, 137).

Several recent studies have demonstrated that the presence of atherosclerotic plaques ≥4mm in the aortic arch is an important new source of emboli to the brain in patients above 60 years of age (138). However, this does not seem to be the case in our young stroke population and is consistent with the results reported from a few previous studies including young as well as old stroke patients (139–141).

More than 70% of patients with spontaneous internal carotid artery dissection and vertebral artery dissections are younger than 50 years and only approximately 8% are 60 years or older (142). A diagnosis of cervicocerebral arterial dissection was established in approximately 20% of our patients, a proportion considerably higher than
reported in most earlier studies (5, 7, 141, 143). Our routine use of posterior circulation angiography revealed that vertebrobasilar dissection was not an uncommon cause of stroke in this age group. This emphasises that a diagnosis of arterial dissection should be considered in all cases of ischaemic stroke in young adults. Generally, patients with a dissection are treated with antiplatelet or anticoagulant regimes to prevent thrombosis within the residual vessel volume. Sometimes surgical repair is indicated. Large randomized trials confirming the appropriateness of these treatments are lacking, and the optimal management strategy remains unknown.

The prevalence of patent foramen ovale and atrial septum aneurysm is increased in younger adults with stroke (144, 145), particularly in patients with otherwise unexplained stroke (137, 146). In those below 45 years of age a prevalence of patent foramen ovale within the same range as in our study (24%-50%) has been reported in three previous studies (140, 146, 147). The mechanism underlying thrombo-embolic events in patients with interatrial septum abnormalities is not well known (137, 148). Angiographic evidence of embolic intracranial arterial occlusions was present in 53% of our patients and gave some evidence of a nidus for thrombus formation. It is of interest to note that 50% of our patients with vertebral dissection had a patent foramen ovale, an atrial septum aneurysm, or both. It is thus important to emphasise that significant vacular pathology has to be excluded before accepting these cardiac abnormalities as the cause of stroke in each individual case.

In our stroke population a hereditary deficiency of natural anticoagulants (protein S and C, antithrombin–III deficiency) was very rarely encountered. This is in agreement with results reported in larger series (5, 149) but at variance with the findings reported from small or selected case series (150, 151). Furthermore the low frequency and low titers of IgG anticardiolipin antibodies in the present study imply that these antibodies do not account for a significant proportion of strokes in young people, at least not in all young stroke populations. These findings are in line with two recent larger prospective studies where the relevance of anticardiolipin antibodies for ischaemic stroke in unselected stroke populations has been questioned (152, 153). However, concerning other haematological causes of stroke, it is possible that factor V Leiden gene point mutation could be of interest, although it is still controversial if activated protein C resistance secondary to this mutation causes arterial vascular disorder (154, 155).

The definition of migraine-induced stroke applied in studies conducted so far has been inconsistent and probably explains why cerebral infarctions in the young attributed to "migraineous infarction" have varied between 1.2% to 25% (10, 17, 156). In the present study only 1% of the patients (one patient), based on the criteria of the International Headache Society (IHS) fulfilled the criteria for migraineous infarction, although the prevalence of migraine with or without aura was higher than might be expected from the background population (157, 158). Based on data from our epidemiological survey the incidence of migraine-induced infarction, meeting the IHS criteria, can be estimated at 0.14/100 000/year with an incidence for possible migraine-induced infarction at 0.7/100 000/year in the age group 18–44 years.
Numerous studies have documented that current use of early generation oral contraception with estrogen content higher than 50 µg is strongly associated with stroke risk (159, 160). The risk increment for cardiovascular disease including stroke among users of oral contraceptives having < 50 µg of estrogen is currently a matter of controversy (161–163). The use of oral contraceptives should probably be avoided in women with diabetes, hypertension, migraine, prior noncerebral thrombotic disease and current smoking (161, 162). By ruling out coexistent and more convincing aetiologies such as cardio-embolism and arterial dissection we could attribute a probable pathogenetic role to oral contraceptive use in 7% of females.

Differential Diagnosis

The main differential diagnosis which infrequently may cause the onset of acute focal neurological symptoms and mimic stroke in young adults is multiple sclerosis (MS) (164, 165). Subclinical evidence of disease can be readily detected by MRI. The question whether some of the 27 patients evaluated in the acute phase with CT-scan only could have been misclassified as stroke when in fact they may have had their first symptoms of MS is therefore relevant. For the following reasons such a misclassification is unlikely to have occurred in our study population: During follow-up eight patients underwent MRI of the brain without any indication of lesions compatible with MS. In eight other patients a vascular pathogenesis was confirmed by angiographic findings. In two cases the vascular pathology was confirmed by autopsy. In nine patients the clinical symptoms (aphasia, hemianopsia) and lesion topography (cortical lesions and lesions affecting thalamus and basal ganglia) were considered inconsistent with typical findings of MS. Furthermore, repeat CT-scanning at follow-up 4 and 12 months after symptom onset disclosed no additional lesions and there was no recurrence of neurological symptoms.

Controls

We used apparently healthy subjects as controls selected from an urban population (paper III–IV). Our controls are thus not expected to be representative for the source population of our patients. For methodological reasons (standardised sampling procedures for evaluation of fibrinolysis and homocysteine metabolism) it was necessary to employ the facilities of the University hospital. It could be argued that the impact on, e.g., PAI-1 and tPA activity of metabolic derangements associated with ischaemic stroke in young adults would be masked when subject selection procedures have enriched metabolic aberrations also in the control group. In this context a healthy control group may be the more appropriate choice. In order to form an idea of how our controls might have differed from the "source population" we compared basic characteristics (systolic and diastolic blood pressure, body mass index, total and HDL cholesterol, triglycerides, smoking habits, and diabetes) of our controls with age-matched subjects selected from the MONICA project. In 1994 a population in the two northernmost provinces of Sweden was screened for
cardiovascular risk factors as a part of the multinational MONICA project. A total of 2 500 individuals in the 25–74 years age range were randomly selected from continuously updated population registers and invited by mail to participate. In total, 1921 subjects (76.8%) participated. By applying an age limit of below 47 years of age, a sample was created with a similar age structure as those of the healthy controls used in the present study. Anthropometric and metabolic variables were used for the subset of individuals which was sampled in the fasting state (approx 2/3 of all participants) while the presence of diabetes or smoking was assessed in the total sample of this age range. No other restrictions were applied and thus this group is truly a randomised population sample which is representative of the general population in this area.

There was no gender specific differences with regard to blood pressure, triglycerides, smoking habits or occurrence of diabetes between our control group and the MONICA study group. Male controls in our study had significantly lower BMI and lower total cholesterol levels versus males from the MONICA population. Among females the only significant difference was lower total cholesterol levels in female controls. In summary the main difference was lower cholesterol levels in our control group. Thus our controls seem to a large extent representative for the source population.

**Fibrinolysis**

Our findings suggest that increased fibrinogen levels and a hypofibrinolytic state, characterized by low tPA activity, high PAI-1 activity and high tPA mass concentrations in baseline samples, may be an important contributing cause of vascular occlusion in young adults.

The results from the prospective Physicians’ Health Study in which a high plasma tPA mass concentration was found to be predictive of stroke in men aged 40 to 84 years (39) is in accordance with our finding that young stroke patients have a hypofibrinolytic state, despite higher than normal tPA mass concentration levels. In elderly stroke populations increased levels of tPA and PAI-1 mass concentration (166) and PAI-1 activity (167) measured in the acute phase remained stable and unchanged at follow-up examination in the convalescent phase. Thus, it is plausible that impaired fibrinolysis preexisted in our stroke patients, and less likely represents a secondary phenomenon to the stroke event. As tPA mass concentration correlated strongly with PAI-1 activity but inversely with tPA activity, it is conceivable that the elevated tPA mass concentration to some extent reflects elevated PAI-1, because tPA mass concentration assays do not distinguish free tPA from tPA which is complexed with PAI-1. Results pertaining to fibrinolytic variables in the various etiological subgroups were quite similar. Thus a generalized abnormality of the fibrinolytic system seems to be present among these patients.

The discrepancy between a reduced tPA activity at baseline, but an increased tPA activity after venous occlusion, as compared to control subjects, could indicate a differential impact of the tPA inhibitor, PAI-1, on activities of tPA at baseline and
after venous occlusion. In line with an hypothesis previously put forward (168), the tPA activity among patients may be suppressed at baseline, since they had a higher baseline PAI-1 activity than the controls. However, after venous occlusion, the impact of PAI-1 on the net tPA activity diminished since the patient group released more tPA into the blood during venous occlusion than did the control subjects. Although the plasma concentration of tPA is dependent on the rate of complex formation with PAI-1, endothelial secretion is also of importance. It is reasonable to assume that a higher secretion rate to some extent also contributed to a higher plasma level of tPA mass concentration. In line with this assumption patients responded with a higher cumulative tPA secretion in response to the venous occlusion test.

Adjustment of baseline tPA and PAI-1 activities for body mass index, cholesterol and triglyceride levels tended to level out the differences between patients and controls. This strongly suggests that the hypofibrinolytic state in young ischaemic stroke patients is largely due to an unfavourable body composition and hyperlipidemia, i.e., changes mimicking those found in the insulin resistance syndrome (42, 169). In contrast to the reduced baseline tPA activity, the difference in tPA mass concentration, both at baseline and after venous occlusion, between patients and controls did not disappear when adjusting for confounding factors. This suggests, in agreement with previous cardiovascular studies (170, 171), that contrary to the tPA and PAI-1 activities, the tPA mass concentration is not just mirroring the presence of an insulin resistance syndrome but may reflect a fundamental difference related to vascular integrity and/or function between patients and control groups.

After correction for other possible cerebrovascular risk factors in a logistic regression model, plasma fibrinogen levels still differed significantly between stroke patients and controls. Thus, in all likelihood, fibrinogen is an independent marker of increased risk of ischaemic stroke in young adults and may be a major contributor to a prothrombotic state in these patients.

We could not find any difference in the levels of vWF between patients and controls. This suggests that the endothelium is intact, or possibly, that circulating vWF levels is not a measure sensitive enough to detect the very early phase of endothelial injury.

**Homocysteine**

The main finding in this study was that the increase in post-load tHcy levels was independently associated with ischaemic stroke after adjustment for established risk factors. In contrast, fasting tHcy levels did not differ between patients and controls. The large size of the effect of homocysteine increase after methionine–challenge in this study may reflect the lack of effect of other more established risk factors in our study population due to the young age of participants.

Most recently a prospective study, restricted to subjects with systemic lupus erythematosus, reported on the association between fasting homocysteine and risk of
stroke in a comparable age group. After adjustment for established risk factors, hyperhomocysteinemia remained an independent risk factor for stroke (172).

In our study a large proportion (23/30 = 76%) of patients with abnormal homocysteine metabolism would have remained undetected by measuring fasting tHcy alone. These results emphasize that a normal fasting tHcy concentration is not synonymous with normal homocysteine metabolism in a young stroke population and that methionine loading is required for the diagnosis of homocysteinemia. Vitamin B₆ deficiency may contribute to an abnormal methionine loading test (173). However, the increase of post–load homocysteine levels in our patients was not explained by a subnormal pyridoxal–5’–phosphate (vitamin B₆) status. In fact, pyridoxal–5’–phosphate levels were higher among patients.

A limitation of all case–control studies is that one cannot rule out the possibility that elevated levels of tHcy may be influenced by the disease, underlying vascular disease or its treatment. Recent data suggest that an acute stroke (166) and myocardial infarction (174) alters levels of tHcy, which could affect the apparent association with risk of disease. Plasma tHcy was found to be lower in the acute phase than in the convalescent phase measured at a median interval of about 1.5 years after the stroke and 6 weeks after the acute myocardial infarction, respectively. Thus, it seems unlikely that this phenomenon can explain our findings of similar fasting tHcy levels in patients and controls because tHcy was measured in the convalescent phase. The behaviour of post–load levels in the acute and convalescent phase after stroke has not been studied.

The post–load tHcy increment was associated with lower tPA activity, higher PAI–1 activity, and independent of conventional risk factors, higher tPA mass concentrations. This may indicate that an interaction with the fibrinolytic system may be one mechanism by which tHcy can provoke thrombembolic events. This is in agreement with an earlier study showing a similar relationship between increased post–methionine load tHcy levels and a significantly increased euglobulin clot lysis time, i.e., corresponding to low tPA activity, and increased PAI–1 activity (175). If these effects are present as a direct effect on endothelial cells is not clear. We did not find high levels of vWF, a marker for endothelial dysfunction, to be associated with post–load tHcy increase above the 90th percentile. This suggests that high plasma levels of homocysteine do not measurably influence the endothelium, or that, possibly, this marker is not sensitive enough to detect the very early phase of homocysteine–induced endothelial injury. Impaired endothelium–dependent–vasodilatation associated with elevated tHcy has been demonstrated in vivo (81, 84). In healthy human volunteers an acute increase in plasma homocysteine after a methionine challenge has been found to be associated with substantial impairment of endothelium–dependent flow–mediated dilatation in an inverse and linear manner (176). The resultant endothelial dysfunction may then eventually contribute to vasospasm and thrombosis.

tHcy levels in the various etiological subgroups did not differ significantly. This indicates that abnormal homocysteine metabolism in premature ischemic stroke is not associated with a particular etiology, e.g., atherosclerosis. However, abnormal homocysteine metabolism under varying circumstances may provide an additional thrombogenic risk, possibly in part mediated by interactions with the fibrinolytic system.
The association of genetic abnormalities in homocysteine metabolism and risk of stroke is inconclusive at present. We found no association between ischaemic stroke and TT genotype, but it is difficult to draw firm conclusions in this respect, taking into account the relatively small number of study subjects.

**Infratentorial infarcts**

Serious complications occurred in the acute phase in patients with large infarcts of the posterior inferior cerebellar artery (PICA) or anterior inferior cerebellar artery (AICA) territory. These data are comparable to studies based on elderly populations. It is generally considered that the long-term prognosis of patients with cerebellar infarction (CI) is fair, provided that the brain stem is unaffected and surgery is not required (108, 177).

In our study, all but two of the patients made a good recovery regarding classical cerebellar and motor deficits. Nevertheless, only 57% of the patients worked full-time one year after the ictus. The patients not returning to work, despite optimal adjustments in their prior occupation, most often attributed their disability and handicap to diffuse symptoms such as headache, tiredness, irritation, anxiety, exhaustion and memory disturbances. An important cause of residual disability influencing work capacity may thus be cognitive deficits.

**COGNITION AND CEREBELLMUM**

Patients performed less well than controls in tasks testing the central, executive domains of working (or short-term) memory. In addition, the patients also performed less well than controls with respect to several measures related to motor speed and integration of visual, spatial and motor skills. In contrast to these alterations, no significant changes were noted regarding intelligence, episodic memory or semantic memory.

The effects of cerebellar lesions on working memory were assessed by means of comparisons between two traditional and presumably less demanding "short-term memory" tasks, digit and word span on the one hand, and the more recent and demanding listening span task. (114). The two former tasks require relatively passive repetition of digits and words, respectively.

Only the performance with respect to the complex, listening span task was affected in a significant way. This result indicates that a complex portion of the human working memory system may be at risk following infratentorial lesions. Hence, the present finding of damage to the working memory system in infratentorial stroke seems well in keeping with functional data obtained in normal subjects (102, 178, 179).

According to Houk (180) the executive components of working memory may be represented by neural activity, held for seconds or minutes and localized in the prefrontal region of the human brain. In his comprehensive review the existence of interconnections between cortical areas (such as the prefrontal cortex) and the
cerebellum was emphasised (180). It was hypothesised that the prefrontal neural activity is regulated and modulated, rather than generated, by cerebellar structures. In this role, its neuronal architecture provides a means of recognizing complex sensory states necessary for the selection and control of action. This process may also explain the common finding, shown in functional neuroimaging studies, of a gradual decline of cerebellar activation with increasing exposure to a cognitive task.

The capacity to cope with spatial demands has been reported to be altered by various cerebellar pathologies (181). The ascending cerebellar projections to areas considered as major parts of the cognitive mapping system, such as the frontoparietal cortex, and their feed-back loops, may be the neural substrates of cerebellar involvement in the processing of spatial information. An interesting aspect of functional neuroimaging studies of the cerebellum is that such studies also have highlighted the involvement of the cerebellum in visual imagery and other visuospatial skills (182). We found that the deficit in coping with visuospatial demands was correlated to the size of the cerebellar lesion. Patients with large cerebellar lesions performed less well than controls or patients with small lesions. Furthermore, a correlation between visuospatial impairment, the neurological disability and maximal working capacity at follow-up was observed. Visuospatial skills have recently been given preeminence in theories about human intelligence (183). In contrast to global intelligence and "crystallised" verbal skills, visuospatial skills are a core constituent of "fluid" intelligence. Fluid intelligence may be directly related to coping and the problem solving skills that are needed in many real life situations (183). Hence, when patients suffer from visuospatial and executive problems, coping and rehabilitative efforts may be affected.

Although the results obtained in this study apparently generate a coherent picture, it could be argued that at least some of the findings could be the result of an involvement of motor skills in the successful execution of some cognitive tasks. However, cerebellar stroke patients performed less well than controls, even in seemingly "motor-free" tasks (e.g., the working memory tasks). Functional magnetic resonance imaging has also shown that attention and motor performance independently activate distinct cerebellar regions (99).

In summary, circumscribed infratentorial lesions impair central aspects of attention and also inflict damage upon visuospatial skills.

WHAT TO DO AND WHEN TO DO IT

Stroke in the young can be a devastating disease and deserves all the skill and the sophisticated technology that can be available in a center of high specialty. Although "the age of the patients with nearly a lifetime left of potential risk of future stroke and other vascular diseases, are factors that argue for extensive evaluation" (184) a "complete" battery of tests is hard to define. The nature and the extent of the
diagnostic testing should be designed to pinpoint the most common causes of stroke in a systematic way applied for all patients and at the same time individualised when clinically relevant.

The diagnosis of stroke is largely clinical and the search for a condition which predisposes the patient to stroke begins with a careful history and physical examination in concert with a series of screening tests. Clinical features and the results of this initial evaluation may direct additional studies. Of patients who present with a stroke-like syndrome, roughly 80% have cerebral infarction, 10% intracerebral haemorrhage, 5% subarachnoid haemorrhage, and 5% another process. The first line of investigations aims at the exclusion of other conditions mimicking ischaemic stroke, e.g., haemorrhage, multiple sclerosis, epileptic seizures, peripheral neuropathy, metabolic disturbances and psychogenic disorders. This is followed by more extensive investigations when the cause of the stroke remains unknown. The first steps in the evaluation are mainly directed at confirmation or exclusion of major arterial or cardioembolic diseases (Table 13).

**NEUROIMAGING**

Neuroimaging is required to make an accurate early diagnosis of stroke. Imaging the brain includes CT or MRI, conventional cerebral angiography, MRI and CT angiography, duplex sonography and transcranial doppler. During the last few years there has been a rapid evolution of anatomical and physiological imaging techniques. In the context of stroke these new techniques provide information about the structure of the brain, the vascular supply of the nervous system and information about the functional state of the brain, including water content, blood flow and metabolism. In particular the usefulness of various MRI techniques has greatly improved.

The MRI technique is helpful in both the diagnosis of an early ischaemic lesion and in the pathogenetic evaluation of stroke. Currently CT is the brain-imaging method of choice for assessment of acute ischaemic injury. Conventional spin-echo MRI has little more to offer than CT, with the possible exception of a clinical presentation suggesting brainstem/cerebellar lesions and the rare cases of cerebral venous thrombosis. After the initial CT scan, MRI is often used to determine the precise location and size of the infarction. The biggest diagnostic yield can be obtained by MRI perfusion and diffusion imaging if available (185). Diffusion-weighted MRI can identify ischaemic tissue within minutes following arterial occlusion (186). MR angiography visualizes large-caliber vessels well, therefore allowing the diagnosis of occlusive disease of the internal carotid artery, or the vertebral and basilar arteries. The complexity of the examination, long acquisition time and susceptibility to movement artifacts may limit the applicability of this technique in the acute phase. However, rapid technologic advances will likely obviate these shortcomings in the near future and as echoplanar imaging and diffusion-weighted imaging become widely available, these techniques may supplant CT scanning as they can be performed within minutes.

The advent of these new non-invasive techniques has limited the use of conventional angiography although cerebral angiography is the gold standard against
FIRST STEP (investigations for major arterial disease)

**Imaging studies**
- Cranial computed tomography
- Magnetic resonance imaging and angiography
- Carotid duplex
- Transcranial doppler
- Conventional cerebral angiography* (if clinical suspicion of intracranial occlusive disease is high or results of the first-time cerebrovascular imaging studies are equivocal)

**Laboratory tests**
- Full blood count, APTT
- Fasting blood glucose/glycosylated Hb
- Liver function, cardiac enzymes
- Serum protein electrophoresis, ESR
- Urinanalysis, Urine drug screen*
- Electrolytes and serum creatinine
- Lipid profile
- Fasting and postmethionine loading tHcy**
- Syphilis and HIV serology*
- CSF investigation*, electrocardiogram

**Outcome.** If a probable cause is established by these routine tests, the diagnostic evaluation is terminated. If not proceed to step 2.

SECOND STEP (investigations for cardioembolic disease haematological and immunological disorders)

- Transesophageal echocardiography with bubble contrast
- Chest X-ray
- Holter monitoring*

**Laboratory tests**
- Anticardiolipin antibodies /Lupus anticoagulant
- Coagulation inhibitory proteins (protein C; protein S;antithrombin-III)**
- APC-resistance**; Factor V (Leiden) mutation analysis
- Anti nuclear antibody, dsDNA, rheumatoid factor, ANCA, ENA, complement factors (C3/C4)
- tPA mass concentration, tPA and PAI-1 activity**
- Blood cultures*

**Outcome.** If the diagnostic evaluation remains negative the evaluation may in selected cases proceed to step 3. For the majority of cases the evaluation is terminated at this stage.

THIRD STEP (other investigational options)

- Skin and muscle biopsy
- Brain biopsy*

**Laboratory tests**
- Serum and CSF lactate
- Mitochondrial DNA analysis*
- Leucocyte alpha-galactosidase A*

**TABLE 13. A STEPWISE DIAGNOSTIC EVALUATION OF ISCHEMIC STROKE IN YOUNG ADULTS.**

*Abbreviations: *, in selected cases; **, in convalescent phase.
which other vascular imaging studies are compared. We used the four vessel angiogram for evaluation of extra and intracranial cerebral vessels. With modern angiographic equipment and access to highly skilled neuroradiologists, conventional angiography carries a small risk of complications (187). In our series no persistent new neurological deficits occurred and other complications were rare. However, MRI and MR angiography or other noninvasive studies (CT angiography, ultrasonic duplex investigation) may be just as informative in the vast majority of cases for evaluating extracerebral vasculature. The role of conventional cerebral angiography is better defined for the evaluation of intracranial vascular anatomy and pathology.

**VASCULOPATHIES**

For the noninvasive diagnosis of atherosclerotic and non-atherosclerotic vasculopathies the implementation of duplex sonography of the neck and MR angiography is suggested as an initial step. Duplex sonography is capable of detecting with sufficient accuracy an occlusive atherosclerotic disease of the extracranial internal carotid arteries. MR angiography is suitable for demonstration of corresponding lesions in the vertebrobasilar area and is also useful as a screening study of the carotid arteries because it tends to exaggerate the degree of stenosis. Therefore the finding of no or mild stenosis on MR angiography indicates the absence of significant carotid pathology.

Internal carotid artery (ICA) dissections typically spare the carotid bulb. Vertebral artery (VA) dissections are most commonly located between C2 and the skull base. Cerebral angiography is the most accurate diagnostic test for ICA and VA dissections. The commonest angiographic abnormalities in ICA dissection are a long tapered segment of ICA narrowing (string sign), aneurysmal pouches, occlusions above the bifurcation in the neck extending toward the skull base, and occasionally a double lumen. The findings in VA dissection are more variable. Similar findings to those seen in carotid dissection may occur, but the string sign is a less consistent finding. Sometimes there may just be an area of localized narrowing (188).

Doppler/duplex scanning has been shown to be a very useful tool in supporting the diagnosis of ICA dissection (189, 190). A sensitivity in the range of 68 – 95% has been reported (190, 191) compared with a sensitivity of 75% in our study. For VA dissections, sonographic studies are less helpful. Combined MRI and MR angiography have however added greatly to the non-invasive work-up of both ICA and VA dissections (192, 193). MRA may show the tapering of the lumen at the dissection and double lumen, but is inferior to conventional angiography in the appreciation of irregularities of the vessel wall (194). However, plain MRI with cross-sectional examinations is often more helpful and is the procedure of choice in suspected dissection. It shows the narrowed vessel lumen and the blood in the wall of the artery, the latter being almost pathognomonic of dissection. MRI/MRA has thus been reported to be reasonably sensitive for detecting dissection although not fully concordant with the angiographic standard (193, 195, 196). If these investigations yield a double lumen or identifies a mural haematom there is no further need to perform a conventional angiography. During the course of recovery, follow-up MRI
and MR angiography may be performed to assess vessel recanalization, which may affect the decision of when to discontinue anticoagulation. CT angiography is another promising non-invasive tool in the diagnosis of ICA dissection (197). These technologic advances have eliminated the need for cerebral angiography in many but not all patients with ICA and VA dissections.

If ultrasonic and MRI/MR angiography investigations are negative and the clinical suspicion of intra- or extracranial occlusive disease is low, cerebral angiography is probably not necessary. However, in a situation with equivocal noninvasive imaging or negative imaging where the clinical suspicion of an arterial dissection or intracranial disease such as vasculitis is high or can not be dismissed, a conventional, contrast angiography is warranted. Conventional cerebral angiography may also be utilized in patients who are uncooperative or claustrophobic. If the diagnosis is established by these routine tests, the diagnostic evaluation is terminated. At this stage approximately 50–60% of the patients will have an undetermined cause of stroke.
CARDIOEMBOLIC DISEASE

In patients with normal cerebrovascular imaging, or in patients with an occluded intracranial artery without a proximal large artery source embolus, echocardiography is recommended.

Cardioembolic mechanisms are particularly frequent in the young (137, 141). In our study minor emboligenic cardiac abnormalities predominated over all other aetiologies (notably patent foramen ovale and atrial septum aneurysm). Transesophageal echocardiography with bubble contrast rather than transthoracic echocardiography, is the preferred procedure because of its higher sensitivity and specificity in detecting cardiac abnormalities. Specific findings which become evident on transesophageal echocardiography but seldom identified by transthoracic echocardiography and which may be helpful in determining the aetiology of an acute ischaemic stroke include left atrial appendage, left atrial or ventricular thrombus, abnormalities of the interatrial septum such as patent foramen ovale and atrial septal aneurysm. After excluding major arterial or cardioembolic diseases, approximately 30% of the patients are left with an undetermined cause.

PROTHROMBOTIC STATES

Haematologic and immunological conditions should be considered in patients with a personal or family history of venous or arterial thromboses, and in patients with an intraluminal carotid or vertebrobasilar clot without underlying occlusive disease or a potential cardioembolic source. Although the significance of antiphospholipid antibodies remains controversial, the use of this test should at least be considered in patients with recurrent fetal loss, thrombocytopenia or lupus erythematosus. The test is also recommended in patients with otherwise normal routine blood tests and normal cerebrovascular imaging.

Since low levels of protein C and protein S may be seen in the acute phase of stroke it is advisable to repeat these tests at least 3 months after the stroke to determine whether the abnormalities persist.

NEW RISK FACTORS

Although elevated homocysteine levels are epidemiologically linked to stroke, the relationship in an individual patient is less certain. If investigation for disturbance in Hcy metabolism is pursued our results support that a methionine loading test is essential and more informative than a fasting value in young stroke patients and to avoid possible acute phase reaction effects the investigation should be performed in the convalescent phase. Treatment with B–vitamins are able to reverse an abnormal homocysteine metabolism, but whether treatment is able to reduce the risk of recurrence or other vascular diseases is unsettled.

Our stroke patients were characterized by a lower tPA activity and higher PAI–1 activity and tPA mass concentration, i.e., a hypofibrinolytic profile. Analysis of these factors may contribute to the overall characterization of an individual patient’s risk
profile and encourage treatment of related metabolic dysfunctions. However, there are no firm data so far that intervention significantly improves the function of the fibrinolytic system or that fibrinolytic markers predict the risk of recurrence in stroke.

If the diagnostic evaluation remains negative more specific investigations may be performed in highly selected cases among those approximately 15–25% of the patients with no obvious explanation for their stroke.

**RARE CAUSES**

Mitochondrial disease may present with stroke in patients under 45 years of age. Estimates of the frequency of mitochondrial DNA defects in the young stroke population vary greatly (between 0.5% and 8%), presumably because of differences in study populations (198, 199). The diagnosis of mitochondrial encephalopathy, lactate acidosis and strokelike episodes (MELAS) should be considered in young stroke cases after other more usual causes have been excluded, in particular in patients suffering occipital stroke. Features such as raised blood and CSF lactate, clinical features (hearing impairment, epilepsy, short stature) and a maternal family history of neurological disease may support a mitochondrial aetiology.

CADASIL, a newly coined acronym for cerebral autosomal dominant subcortical arteriopathy with ischaemic leukoencephalopathy, is recognised as a cause of hereditary multi-infarct dementia (200). In the earlier stages of the disease, affected individuals may experience stroke before the age of 45 years. CADASIL should be suspected in patients with unexplained subcortical ischaemic strokes, whenever they are associated with MRI signal abnormalities in white matter and basal ganglia. These findings should prompt a genealogical study including all first- and second-degree relatives. At this stage many other unusual conditions may be taken into consideration but only very rarely substantiated.

**Concluding remarks**

Dealing with stroke in young patients is one of the most challenging tasks for neurologists, because therapeutic willingness is maximal in these cases but is often frustrated by an elusive aetiology. During the course of an extensive evaluation, it is often uncertain whether the results of these investigations in a significant way alter the management and prognosis of these patients (e.g., an isolated finding of a patent foramen ovale or the presence of anticardiolipin antibodies). Unravelling the cause of stroke in the many cases with undetermined aetiology is one of the most important challenges that researchers and clinicians involved in stroke management have to face in the near future. Regardless of whether the diagnostic evaluation identifies a specific cause or not, it is therefore of utmost importance to institute aggressive control of concomitantly present risk factors such as hypertension, smoking, hyperlipidemia and overweight. It is also imperative to delineate and ameliorate the consequences of the brain damage caused by a stroke in terms of disability and handicap including cognitive dysfunction. In the work-up of these patients a dedicated neuropsychological evaluation will prove helpful in assisting an optimal rehabilitation.
Conclusions

1.1 After superior sagittal sinus thrombosis in young adults, hydrodynamic abnormalities, particularly raised cerebrospinal fluid pressure mainly due to raised sagittal sinus pressure, persists for many years and only gradually decline.

1.2 The change in conductance or cerebrospinal fluid resorption facility plays only a minor part in the increase in intracranial pressure.

2.1 The incidence rate for ischaemic stroke in Northern Sweden is higher than previously reported from most countries in Western Europe.

2.2 The higher incidence is not explained by a higher prevalence of premature atherosclerotic vasculopathy.

2.3 Nontraumatic arterial dissection is a leading cause of ischaemic stroke.

2.4 In spite of extensive investigation the cause of stroke remain undetermined in one fifth of the patients. Without the additional diagnostic information derived from advanced cardiac imaging, the proportion of indeterminate cases would have constituted 37% of the patients.

3.1 Increased fibrinogen levels and tissue plasminogen activator mass concentration are independently associated with ischaemic stroke in young adults.

3.2 Metabolic perturbations are closely interrelated with tissue plasminogen activator and plasminogen activator inhibitor type 1 activity.

4.1 Moderately elevated increase of total homocysteine levels after methionine loading may provide an additional thrombogenic risk factor for stroke in young adults, partly mediated by interactions with the fibrinolytic system.

4.2 There is no association between ischaemic stroke in young adults and the C677T mutation in methylenetetrahydrofolate reductase gene.

5.1 Cognitive disturbances occur in association with circumscribed infratentorial (mainly cerebellar) lesions.
5.2 Cerebellar damage impairs central aspects of attention and working memory, and affects visuospatial skills. In contrast, intelligence and episodic memory remain unaltered.

5.3 The outcome is favorable in terms of neurological deficits, but cognitive disability may course significant problems in resuming former employment.


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