Acute ischemic stroke

Factors that predict outcome

Titto T Idicula, MD

The degree philosophiae doctor (PhD)

University of Bergen, Norway

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Institute of Clinical Medicine, University of Bergen
Department of Neurology, Haukeland University Hospital, Norway

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Papers included in the thesis

The thesis is based on the following papers:

1. Idicula TT, Naess H, Thomassen L. The Prevalence and Significance of Microembolism in Acute Stroke Patients: A Prospective Study. BMC Neurology (submitted)

2. Idicula TT, Waje-Andreassen U, Brogger J, Naess H, Lundstadsveen M.T, Thomassen L. The Effect of Physiologic Derangement in Patients with Stroke Treated with Thrombolysis. Journal of Stroke and Cerebrovascular Diseases, Vol. 17, No. 3 (May-June), 2008: pp 141-146

3. Idicula TT, Waje-Andreassen U, Brogger J, Naess, Thomassen L. Serum Albumin in Ischemic Stroke Patients: The Higher the Better. Cerebrovascular Disease 2009; 28(1):13-7.

4. Idicula TT, Brogger J, Naess H, Waje-Andreassen U, Thomassen L. Admission C - reactive protein after acute ischemic stroke is associated with stroke severity and mortality: The `Bergen stroke study`. BMC Neurology 2009 Apr 28;9:18.

List of abbreviations

AHA	American Heart Association
BI	Barthel Index
CBC	Complete blood count
CE-MRA	Contrast-enhanced magnetic resonance angiography
CRP	C-reactive protein
CT	Computer tomography
CTA	CT angiography
DUS	Duplex ultrasound scan
DWI	Diffusion weighted imaging
FDA	Food and drug administration
ICA	Internal carotid artery
IMT	Intima media thickness
LACI	Lacunar infarct
MCA	Middle cerebral artery
MES	Microembolic signals
MR	Magnetic resonance
MRA	MR angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institutes of Neurological Disorders and Stroke
OCSP	Oxfordshire Community Stroke Project
PACI	Partial anterior circulation infarct
POCI	Posterior circulation infarct
SITS-MOST	SITS-Monitoring Study
TACI	Total anterior circulation infarct
TCD	Transcranial Doppler
TCCD	Transcranial colour coded Doppler
TEE	Transoesophageal echocardiography
TIA	Transient ischemic attack
TOF-MRA	Time of flight magnectic resonance angiography
TOAST	Trial of Org 10172 in Acute Stroke Treatment
tPA	Tissue plasminogen activator
WHO	World Health Organisation

Introduction

Background

Vascular disorders accounts for the major cause of mortality in the world (WHO. World Health Report 2002, Annex Table 2. World Health Organization, 2002:186-91). Ischemic stroke is second only to coronary artery disease as the major cause of mortality. Ischemic stroke is the end result of occlusion of a blood vessel supplying the brain by a thrombus originating somewhere outside the brain or as a result of a thrombotic stenosis of a cerebral blood vessel itself. The major risk factors for stroke in the western world include hyperlipidemia, hypertension, diabetes mellitus and smoking. Knowledge about these risk factors led to interventions and preventive measures that reduced the incidence of stroke during the last two decades (Rothwell, Coull et al. 2004). However, many risk factors are yet to be identified since stroke etiology is not identified in a large proportion of ischemic stroke patients.

Clinical Diagnosis

Clinical symptoms of ischemic stroke depend on the anatomical location of the thrombus. Stroke usually presents with an acute loss of brain functions. These functions usually involve the realm of motor, sensory, language, vision, visuo-spatial perception or consciousness. Most ischemic strokes presents as a sudden loss of function in one of the above domains. However, a sudden loss of neurological functions in the above domains could represent pathologies other than ischemic stroke. These include intracranial hemorrhage, seizures, vasovagal syncope, migraine, tumor, meningitis etc.. Clinical examination along with neuroimaging secures a proper diagnosis of ischemic stroke.

Neuroimaging

Neuroimaging modalities used for stroke include structural imaging such as non-contrast computerised tomography (CT) scan, magnetic resonance imaging (MRI), positron emission topography (PET) scan, CT perfusion imaging and MR perfusion imaging and arterial imaging such as CT angiogram, MR angiogram and conventional angiogram.

Non-contrast CT scan of head is usually the initial investigation of choice. The initial CT scan is used to rule out intracranial hemorrhage or other obvious non-infarct disorders such as tumor. The sensitivity of CT scan to detct infarct is about 66% with a specificity of 87%, if performed within the first 6 hours after symptom onset (Wardlaw and Mielke 2005). However, the sensitivity falls even lower when CT scan is performed within the first 3 hours after symptom onset. Nevertheless, CT scan remains as most commonly employed imaging modality in acute stroke patients.

While both MRI and CT scan have the same sensitivity to detect hemorrhage, MRI is a better neuroimaging modality because it is more sensitive in detecting ischemic stroke in the first hours, especially in the posterior circulation (Chalela, Kidwell et al. 2007). Diffusion weighted imaging (DWI) is a useful technique to identify an infarct minutes after stroke onset. The size of DWI lesion largely corresponds to the volume of infarct. However, DWI lesion by itself cannot be substituted for a clinical stroke severity score (Hand, Wardlaw et al. 2006). Still, MRI is a very useful tool to identify the location of lesion and to classify the stroke etiology.

Perfusion images are increasingly available for assessment of acute ischemic stroke. Perfusion images are used to identify the penumbra – the tissue at risk for infarction, but still salvageable. Though it is more time consuming and expensive than a non-contrast CT scan, perfusion CT scan offers opportunity to assess penumbra with high sensitivity, specificity and accuracy (97.0%, 97.2%, and 97.1%, respectively) (Murphy, Fox et al. 2006). MR perfusion and PET scan are alternative modalities to assess the penumbra

Arterial imaging in stroke is important to recognize the involved artery and to provide appropriate treatment. Arterial imaging involves imaging of both the extracranial carotid and vertebral arteries and the imaging of intracranial vessels. Imaging of extracranial carotid arteries can be done by both invasive method (conventional angiography) and non-invasive methods. With careful planning, non-invasive methods can replace invasive methods (Wardlaw, Chappell et al. 2006).

Non-invasive arterial imaging can be performed with duplex ultrasound scan (DUS), magnetic resonance angiography (MRA) and CT angiography (CTA). DUS have demonstrated a sensitivity of 98% and a specificity of 88% for detecting > 50% internal carotid artery (ICA) stenosis; and 94% and 90% respectively for detecting >

70% ICA stenosis (Jahromi, Cina et al. 2005). The drawback of DUS is that it is highly operator-dependent.

MRA can be done with or without contrast. The technique used for non-contrast MRA is time-of-flight imaging (TOF-MRA). TOF-MRA relies upon the movement of magnetized blood. This method provides high sensitivity and specificity; however there is more likelihood for patient movement artifact because the image acquisition time is longer. Contrast enhanced MRA (CE-MRA) relies upon the presence of contrast within the lumen. This method tends to overestimate the degree of stenosis. Both the techniques have somewhat similar sensitivities but CE-MRA has less specificity in comparison to TOF-MRA (Jaff, Goldmakher et al. 2008).

CT angiogram (CTA) always involves the use of contrast and therefore has the disadvantage of using iodinated contrast. However, CTA offer better spatial resolution than MRA. It has an overall sensitivity of 97% and specificity of 99%. Arterial imaging is important both in the acute phase and for the etiological work-up of ischemic stroke. Occasionally, stroke patients with thrombus in a major artery can present with minimal symptoms (Idicula and Thomassen 2009). Figure 1 shows the presence of a thrombus at the M2 segment of middle cerebral artery (MCA) in a patient with normal neurological examination at the time of admission. This detection of such thrombus is important for the proper management, i.e. intravenous thrombolysis in this case.

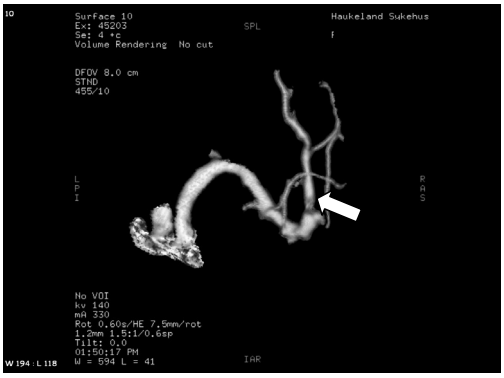

Figure 1. CT Angiography at the time of admission, showing thrombus at M2 segment of right MCA.

Neurosonology

The two types of diagnostic ultrasound examinations used in stroke patients are blind Doppler scan and duplex scan. Blind Doppler scan uses the Doppler principle for the measurement of blood flow velocity in an artery. Blind Doppler is used for assessing intracranial hemodynamics and thereby indirectly the vasculature. It can also be used for the detection of microemboli. The prevalence of microemboli in ischemic stroke varies from 5.7% to 56% in different studies (Delcker, Schnell et al. 2000; Poppert, Sadikovic et al. 2006). It is not yet clear whether the presence of microemboli is important for predicting outcome. However, the detection of microemboli may improve current ischemic stroke subtype classification (Lund, Rygh et al. 2000).

Duplex ultrasound combines gray scale B mode imaging of anatomical structures along with color Doppler for the real time measurement of blood flow and flow velocities. It can be used for imaging of both the extracranial as well as intracranial vasculature. Duplex scan is indicated for both transient ischemic attack (TIA) and ischemic stroke (Jaff, Goldmakher et al. 2008). Gray scale B mode allows imaging of intima media thickness (IMT) and atherosclerotic plaque. Plaque can be classified according to hemodynamic alteration, surface characteristics and echogenicity. Table 1 shows one of the classification based on these characteristics (Thiele, Jones et al. 1992) .

Hemodynamic (% Stenosis Diameter)	Morphologic	By Surface
H1, mild (<50%)	P1, homogeneous	S1, smooth
H2, moderate (50%–69%)	P2, heterogeneous	S2, irregular (defect <2 mm)
H3, severe (70%–95%)		S3, ulcerated (defect >2 mm)
H4, critical (95%–99%)		
H5, occluding (100%)		

Table 1. Classification of plaque morphology based on Duplex scan (Thiele, Jones et al. 1992)

Laboratory work-up

Acute ischemic stroke patients are recommended to undergo the following tests at a minimum; Serum glucose, serum electrolyte level, complete blood count

(CBC), routine urine analysis and coagulation studies (Messe and Jauch 2008). The laboratory tests are done to rule out stroke mimickers and to assess the feasibility of thrombolytic treatment. Apart from these routine tests, C-reactive protein (CRP) and serum albumin may be tested to assess the inflammatory status and nutritional status of the patients. CRP and phospholipase A2 can be used as inflammatory marker that may predct outcome (Elkind 2009). Other laboratory work-up includes a search for the etiology of stroke that may include, anti-phospholipid antibody, ANA, RPR, vitamin B12 level, homocysteine level, factor V Leiden, anti-thrombin level and lipid profile.

Etiology of ischemic stroke

Trial of Org 10172 in Acute Stroke Treatment (TOAST) is one of the most commonly used classification to subtype ischemic stoke based on etiology (Bamford, Sandercock et al. 1991). Based on clinical features and baseline CT scan, stroke etiology is classified into: large-artery atherothromboembolic, cardioembolic, small-vessel thrombotic, other etiology, or undetermined etiology. It has shown to have an accuracy of 62% (Madden, Karanjia et al. 1995). However, a substantial number of patients remain under the category of `unknown´ etiology.

Treatment of acute ischemic stroke

Stroke treatment was revolutionized with the introduction of tissue plasminogen activator (tPA) for intravenous thrombolysis. One of the earliest studies that showed significant clinical benefit was NINDS study (Shieh, Shiang et al. 1995). This lead to the food and drug administration (FDA) approval for the use of tPA in USA. Following that two other major studies in Canada and Europe also proved its safety (Hill and Buchan 2005; Wahlgren, Ahmed et al. 2007). Figure 2 shows results from a pooled analysis of three major studies. The odds ratio for favourable outcome increased as the interval from stroke onset to start of treatment decreased (Hacke, Donnan et al. 2004).

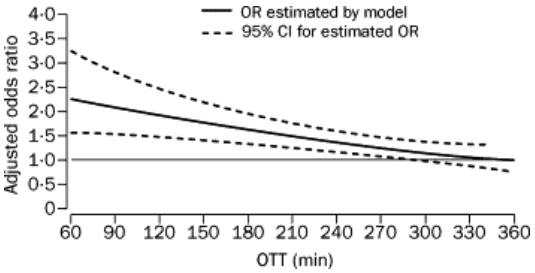

Figure 2. OR for favourable outcome after intravenous thrombolysis (Hacke, Donnan et al. 2004)

Because of the decreasing efficiency and fear of hemorrhage, intravenous thrombolysis was initially approved only for the first 3 hours after symptom onset. However, a recent large study shows that intravenous thrombolysis is relatively safe up to 4.5 hours (Hacke, Kaste et al. 2008).

Supportive therapy for acute ischemic stroke

Apart from the thrombolytic therapy, supportive measures are very important in the acute phase. Both animal and human studies have shown that factors such as high body temperature and high blood glucose may have deleterious effect on stroke outcome (Meden, Overgaard et al. 1994; Wang, Lim et al. 2000; Williams, Rotich et al. 2002; Baird, Parsons et al. 2003; Suzuki, Bramlett et al. 2004). The current guidelines from American Heart Association (AHA) recmmends treating hyperthermia with anti-pyretics and hyperglycemia with insulin (Adams, del Zoppo et al. 2007). Apart from that, measures such as hypothermia and blood pressure control are also under trial.

Neuroprotection

Neuroprotection refers to the process of protecting neurons from apoptosis and ischemic degeneration. At present no neuroprotective agents are proven to have a definite effect in stroke patients. A number of agents have been tried with disappointing results. A few agents that were tried include NMDA receptor antagonist, GABA agonist, magnesium, phospholipid precursors like citocoline and antioxidant spin trap (Ginsberg 2008). Apart from that, many other agents including serum albumin are also currently under trial (Ferro and Davalos 2006).

Stroke outcomes and predictors of outcome

Stroke is a devastating disorder causing death and disability. The average case fatality rate one month after stroke onset is about 23% and it rises to about 30% in 6 months and about 50% in one year (Hankey, Jamrozik et al. 1998; Hankey, Jamrozik et al. 2000). The most common causes of mortality after discharge from hospital are recurrent cerebrovascular disease, pneumonia and heart disease (Kimura, Minematsu et al. 2005). The functional outcome after stroke is most commonly measured by modified Rankin scale (mRS) (Rankin 1957) and Barthel index (BI) (Mahoney and Barthel 1965) (See index).

The best predictors of prognosis after stroke are the initial neurological deficit and the age of the patient. Other factors that affect prognosis are high blood glucose, high body temperature, and previous stroke (Weimar, Ziegler et al. 2002). Medical complications are another key determinant of prognostic outcome and length of hospital stay after stroke (Saxena, Koh et al. 2007). Among different subtypes of stroke, cardioembolism shows the highest mortality while large artery atherosclerosis carry the highest stroke recurrence rate (Petty, Brown et al. 2000).

Aims of the thesis

1. To assess whether microemboli detected by transcranial Doppler in acute ischemic stroke are associated with stroke outcomes.

   We hypothesised that microemboli are highly prevalent in thromboembolic stroke and microemboli burden is associated with poor prognosis. This hypothesis is discussed in paper 1.

2. To assess how certain clinical (blood pressure and body temperature) and laboratory parameters (blood glucose) are associated with stroke outcome in patients who undergo intravenous thrombolysis.

   We hypothesised that high blood glucose, high body temperture and high blood pressure both before and after thrombolysis are associated with poor outcome. This hypothesis is discussed in paper 2.

3. To assess how laboratory parameters like CRP and albumin can influence outcome in acute ischemic stroke.

   We hypothesised that high CRP is associated with poor outcome and increased future vascular events. We hypothesized that high albumin is associated with better outcome and lower mortality. This hypothesis is discussed in paper 3 & 4.

Material and methods

The data for all the papers were obtained from the Department of Neurology, Haukeland Hospital. The Department of Neurology has a stroke unit where all stroke patients <60 years of age and half of patients >60 years of age were admitted until June 2007. From June 2007, all patients with acute stroke regardless of age were admitted to the stroke unit.

The data for papers I, III and IV were obtained from the ´Bergen stroke study´ registry. The registry was started in February 2006. After obtaining consent from patients, details including patient demography, clinical findings, laboratory and radiological findings and outcome were registered in the registry. The study was approved by the local ethical committee and the national ethical committee (NSD - Norsk Samfunnsvitenskapelig Datatjeneste).

The data for paper II was collectively systematically from all patients admitted with ischemic stroke and underwent intravenous thrombolysis during the period 1998-2006.

Neurological evaluation

All the patients underwent neurological evaluation by a junior physician in the emergency room. The clinical evaluations that include physiological parameters such as blood pressure, pulse and temperature and National institute of health stroke scale (NIHSS) were performed at the emergency room. After undergoing non-contrast CT scan of head, the patients were admitted to the department´s comprehensive stroke unit for close monitoring of the above parameters on a timely interval. The patients received appropriate treatments such as intravenous thrombolysis and anti-thrombotics in the stroke unit. A stroke neurologist further evaluated the patients on the following day.

Neurosonological evaluation

Patients included in paper I underwent transcranial Doppler (TCD) microemboli monitoring using Pioneer Nicolet 8080 system. Microemboli monitoring

was done for one hour using two 2-MHz probes attached to head with the help of a headband. Using trans-temporal bone window, signals from both the middle cerebral arteries (MCA) were obtained by manual search. The signals from the proximal part of MCA were used for microemboli monitoring. The machine was set at the lowest gain possible. The machine was set for automatic detection of microemboli. The automatically detected microemboli were manually evaluated offline (investigators TTI and LT) to rule out artifacts. Microemboli were defined using the criteria drawn up by the Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium (Table 2) (1995). One investigator (TTI) performed all theTCD microemboli monitoring.

Micrombolic signals should be transient (lasting <300 milliseconds)
Microembolic signals must be least 3 dB higher than the background blood flow signal
Unidirectional within the Doppler spectrum
Accompanied by an audible ‘snap’, ‘chirp’, or ‘moan’

Table 2. Criteria used to define microemboli (Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium)

All patients included in Papers I-IV underwent duplex ultrasound examination of extracranial carotid arteries, using Philips IU22. Stenosis of internal carotid artery was classified as <50%, 50-70%, 70-99% and occlusion based on modified NASCET criteria (Fig 3).

$$\text{Area-stenosis \%} = \frac{PSV_{stenosis} - PSV_{distal\ ICA}}{PSV_{stenosis}} \times 100$$

Figure 3. Modified NASCET criteria used to grade degree of stenosis
PSV stenosis = Peak systolic velocity in the area of maximum stenosis
PSV distal ICA = Peak systolic velocity distal to stenosis

Laboratory evaluation

At the time of admission blood was collected for measuring blood glucose, C-reactive protein (CRP) and serum albumin. The blood glucose was measured using

Gluco-quant method (Roche Diagnostics). CRP was measured by Tina-quant latex method using Modular P (Roche Diagnostics). Serum albumin was measured using Albumin BCG method (Roche Diagnostics). Those patients with a history of diabetes mellitus and those patients with blood glucose above 8 μmol/ L had blood glucose measurement 6 times during the first 24 hours after admission and 4 times during the following days.

Stroke classifications

All patients were classified into diffrent stroke groups based on TOAST classification and OCSP classification. A stroke neurologist performed classification after completing stroke work-up.

TOAST Classification

TOAST classification categorize ischemic stroke based on etio-pathology. Etio-pathology of stroke was determined based on clinical examination, neuroimaging with CT or MRI, vascular imaging using angiography or ultrasound and cardiac investigations. Ischemic stroke patients are classified into following sub-groups: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology, including those with more than one possible etiologies.

OCSP Classification

OCSP classification describes the anatomical localization of infarct based on clinical subgroups (Bamford, Sandercock et al. 1991). Ischemic stroke is classified into following sub-groups: 1) total anterior circulation infarct (TACI), 2) partial anterior circulation infarct (PACI), 3) posterior vcerebral infarct (POCI) and 4) lacunar infarct (LACI).

Follow-up

Stroke outcomes were measured by modified Rankin scale (mRS), Bartel ADL index (BI), long-term mortality and future vascular events. For papers III, IV,

and I, mRS was measured 7 days after stroke onset or at discharge, if discharged earlier, by a specialised stroke nurse. For paper IV, both BI and mRS were measured for analyzing functional outcome. For paper II, mRS was measured 3 months after stroke onset. Survival outcome was measured in papers I, III and IV. Patients were followed up a maximum of 2 years and all causes of mortality were registered. Data for mortality were obtained from the Norwegian national registry (Norsk Folkeregister). Future vascular events were analysed in papers IV and I. These vascular events were obtained from searches of the electronic discharge diagnosis registry at the hospital using ICD10 codes I20, I21, I22, I63, G45 (excluding G454), I61, and I74. These electronic events were then manually validated for quality control by checking patient´s hospital records.

Summary of the papers

Paper 1

The Prevalence and Significance of Microembolism in Acute Stroke Patients: A Prospective Study.

Idicula TT, Naess H, Thomassen L.
BMC Neurology (Submitted)

Background: Etiologic diagnosis of stroke is important for implementing a proper therapeutic strategy. Microembolic monitoring might be useful for a better classification of stroke and to predict prognosis. The aim of our study was to determine the prevalence of MES, the different factors associated with the presence of MES and the association between MES and outcomes in stroke patients presenting within 24 hours after the onset of symptoms.

Methods: The study was conducted from October 2006 to December 2008. Acute ischemic stroke patients admitted within 24 hours after stroke onset were included in the study whenever possible. MES detection of both the middle MCA was done for a period of 1 hour using 2-MHz probes applied over trans-temporal window. Microemboli were automatically detected by machine and later confirmed manually.

Results: Fifty-four patients were included during the study period. The mean age of the patients was 67.8 years. The prevalence of either ipsi-lateral or contra-lateral microemboli was 18.5% (n=10). Microemboli were strongly associated with embolic stroke (large-artery atherosclerosis and cardioembolism on TOAST classification) (OR 8; p=0.03). Eight out of 10 patients with microemboli had either large-artery atherosclerosis or cardioembolic stroke. Microemboli were not associated with short-term functional outcome, long-term mortality or future vascular events.

Conclusions: Microemboli are moderately frequent following acute ischemic stroke. Microemboli monitoring helps to better classify stroke type. Microemboli do not help to predict prognosis.

Paper 2

The Effect of Physiologic Derangement in Patients with Stroke Treated with Thrombolysis

Idicula TT, Waje-Andreassen U, Brogger J, Naess H, Lundstadsveen M.T, Thomassen L.

Journal of Stroke and Cerebrovascular Diseases, Vol. 17, No. 3 (May-June), 2008: pp 141-146

Background: The interaction between body temperature, blood glucose, and blood pressure and outcome in acute ischemic stroke patients treated with thrombolysis is not clearly studied. The aim of this study was to assess the influence of these factors before and after thrombolysis on outcome.

Methods: From 1998 to 2006, we prospectively studied 127 patients who received intravenous thrombolysis for acute stroke. Following parameters were measured both before and after thrombolysis: body temperature, blood glucose and blood pressure. Stroke outcome was measured with mRS 3 months after the index stroke.

Results: The mean body temperature before and after thrombolysis were 36.5± 0.66^0 C and 36.6± 0.79^0 C respectively. Body temperature before thrombolysis was not associated with outcome whereas high body temperature after thromlysis was associated with poor outcome (OR 0.79, p= 0.5; OR 2.84, p= 0.01). The mean blood glucose before and after thrombolysis were 6.7±1.9 mmol/L and 6.9±2.7 mmol/L respectively. Blood glucose before thrombolysis was not associated with outcome whereas high blood glucose after thrombolysis was associated with poor outcome (OR 1.04, p= 0.08; OR 1.33, p= 0.03). The mean systolic blood pressure both before and after thrombolysis was 156 ±23 mm Hg and 172±25 mm Hg respectively. High systolic blood pressure both before and after thrombolysis was associated with poor outcome (OR 1.27, p= 0.025; OR 1.22, p= 0.045). The mean diastolic blood pressure before and after thrombolysis were 84±17 mm Hg and 97±16mm Hg respectively. Diastolic blood pressure both before and after thrombolysis was not associated with outcome.

Conclusions: In ischemic stroke patients, frequent monitoring of body temperature and blood glucose and the appropriate treatment of it, if elevated, are important during the phase following thrombolysis. However in the hyper-acute phse, before thrombolysis, reduction of high systolic BP is important.

Paper 3

Serum Albumin in Ischemic Stroke Patients: The Higher the Better

Idicula TT, Waje-Andreassen U, Brogger J, Naess, Thomassen L.
Cerebrovasc Disease 2009; 28:13-17.

Background: The aim of this study was to assess the neuroprotective role of serum albumin in ischemic stroke patients and to find out if evidence from animal studies can be translated into clinical stroke.

Methods: from February 2006 to March 2008, we prospectively studied 444 ischemic stroke patients. Serum albumin was measured at the time of admission. Acute stroke severity was scored with NIHSS. Functional outcome was measured with modified Rankin scale (mRS) obtained 7 days after admission. Survival outcome was measured by assessing mortality during 2-year follow-up. The national registry was used to assess data on mortality. The association between albumin and outcomes were analysed with logistic regression after adjusting for confounding factors.

Result: The mean age of the patients were 70.4 (14.4) years. The median NIHSS on admission was 4 and the median mRS was 2. Sixty patients (13%) died during the two-year follow-up. High albumin was independently associated with a better functional outcome (OR 1.12, 95% CI 1.05-1.20, p=0.001). On Cox regression analysis, after adjusting for age sex and NIHSS at admission, high albumin was associated with a lower mortality (OR 0.88, 95% CI 0.83-0.93, p= 0.000).

Conclusion: This study indicates that high albumin is independently associated with a better outcome and lower mortality in ischemic stroke patients. This findings confirms data from animal studies that albumin is neuroprotective in ischemic stroke.

Paper 4

Admission C - reactive protein after acute ischemic stroke is associated with stroke severity and mortality: The `Bergen stroke study`

Idicula TT, Brogger J, Naess H, Waje-Andreassen U, Thomassen L.
BMC Neurology. 2009 Apr 28;9:18.

Background: Previous studies in ischemic stroke patients show that CRP, an inflammatory marker, is associated with stroke outcomes and future vascular events. It is not clear whether this is due a direct dose-response effect or rather an epiphenomenon. The aim of this study was to assess whether high CRP in acute ischemic stroke is associated with functional outcome, mortality and future vascular events.

Methods: From February 2006 to September 2008, we prospectively studied 498 ischemic stroke patients who were admitted within 24 hours after the onset of symptoms. CRP and NIH stroke scale (NIHSS), were measured at the time of admission. Aetiology of stroke was assessed by TOAST criteria. Short-term functional outcome was measured using mRS and Barthel ADL index (BI) 7 days after admission. Patients were followed for up to 2.5 years for long-term mortality and future vascular events data.

Results: The median CRP at admission was 3 mg/L. High CRP was associated with with high NIHSS (p=0.02) and high long-term mortality (p=0.002) even after adjusting for confounding variables. High CRP was associated with poor short-term functional outcomes (mRS >2; BI <95) (p=0.01; p=0.03). However, the association was not significant after adjusting for confounding variables including NIHSS (p=0.98; p=0.88). High CRP was not associated with future vascular events (p=0.98).

Conclusion: Admission CRP is associated with stroke severity and long-term mortality when measured at least 24 hours after onset. There is a crude association between high CRP and short-term functional outcome which is likely secondary to stroke severity. CRP is an independent predictor of long-term mortality after ischemic stroke.

Discussion

Acute phase of ischemic stroke

The term ”acute phase” is a rather loosely defined. It includes 24 hours following the onset of symptom onset. This is the most important phase because neurons die at an alarming rate during this phase. Apart from that, interventions to prevent neuronal death are most effective during the acute phase. Clinical examination, laboratory work-up, radiological and sonographic investigations are important and needs to be done promptly. All the papers included in the thesis involve analysis of various factors measured during the ”acute phase” that are associated with outcome.

Clinical assessment of acute stroke

All ischemic stroke patients included in the study were examined by a junior neurologist in the emergency room. None of the patients were clinically examined by the investigator (TTI) and the clinical findings were unknown to the investigator. Investigator bias was thereby eliminated.

Stroke severity assessment

NIH stroke scale (NIHSS) was assessed in the emergency room to help determine the appropriate treatment. NIHSS was measured regularly during the first 24 hours, at 24 hours after admission, and at discharge. Previous studies have shown that NIHSS is a significant predictor of outcome and a significant predictor of complications such as secondary hemorrhage (Adams, Davis et al. 1999; DeGraba, Hallenbeck et al. 1999). When assessing stroke outcomes, stroke severity is a confounding factor. Therefore, we included the NIHSS at admission in the analysis in order to adjust for confounding effects. In certain studies, improvement in NIHSS between admission and discharge is used for assessing outcome as well. However we used other outcome measures such as mRS and BI for assessing outcome as in NINDS study (Adams 1995). NIHSS was categorized as low, medium and high severity in papers I, III and IV but NIHSS was analyzed as a continuous variable in paper II.

OCSP classification was also used to indirectly assess stroke severity (Bamford, Sandercock et al. 1991). OCSP classification stratifies patients as total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI) and posterior circulation infarct (POCI). The classification is performed by clinical criterion alone. It is shown to have up to 75% correlation with radiologically identified infarcts (Anderson, Taylor et al. 1994; Lindgren, Norrving et al. 1994; Wardlaw, Dennis et al. 1996; Mead, Lewis et al. 2000). However, the reliability in defining the vascular pathology at admission using OCSP is less than 50% (Thomassen, Waje-Andreassen et al. 2006). Although OCSP does not a directly measure stroke severity, it is good predictor of stroke outcome (best with LACI, worst with TACI) (Sprigg, Gray et al. 2007). Paper III and IV showed that OCSP was associated with stroke outcomes and the variables of interest (CRP and serum albumin).

Temperature measurement

Many observational studies have shown a negative association between body temperature and outcome following ischemic stroke (Jorgensen, Reith et al. 1996; Castillo, Davalos et al. 1998; Boysen and Christensen 2001). We measured body temperature at the time of admission and daily for the first 5 days. An analysis of our data collected from all stroke patients admitted during the years 2006 and 2007 showed that patients presented with high mean body temperature and the mean body temperature dropped during the following days (Figure 4). The pattern was similar among patients who underwent intravenous thrombolysis and those who did not undergo thrombolyis. However, the mean body temperature of thrombolysed patients was higher than non-thrombolysed patients at any given time points. Patients who underwent thrombolysis had a higher NIHSS than patients who did not undergo thrombolysis. A previous study has shown that body temperature is higher in patients with a higher stroke severity (Boysen and Christensen 2001), which may explain this finding in our study.

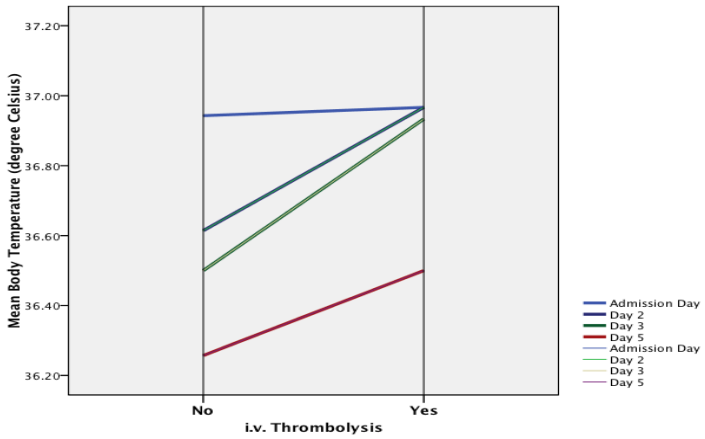

Figure 4. Shows the difference in mean body temperature (degree Celsius) among patients who underwent i.v thrombolysis and those who did not undergo thrombolysis.

It is therefore important to know how body temperature at different time points influence outcome in stroke patients. We analyzed how body temperature affects outcome both before and after thrombolysis (paper II).

Blood Pressure

Presence of hypertension before stroke may not be a predictor of outcome after stroke (Feigenson, McDowell et al. 1977; Caronna and Levy 1983; Henley, Pettit et al. 1985). However some studies contradict this finding and have shown that hypertension is a predictor of outcome after stroke (Carlberg, Asplund et al. 1991). Similar controversy exist about the management of high blood pressure after ischemic stroke (Spengos, Tsivgoulis et al. 2006). Studies on patients treated with thrombolysis (Brott, Lu et al. 1998) and not treated with thrombolysis (Phillips 1994; Castillo, Leira et al. 2004) have shown that lowering blood pressure after stroke adversely affect outcome. Current guidelines recommend withholding antihypertensive therapy during the acute phase of stroke unless the diastolic blood pressure exceeds 120 mmHg or the systolic blood pressure exceeds 220 mm Hg in patients who are not candidates for rt-PA (Adams, del Zoppo et al. 2007). For patients who are treated with thrombolysis the threshold for treatment is set at a lower blood pressure of 180/105 mm Hg because of the risk for developing secondary hemorrhage. Figure 5 shows the number of patients who developed secondary hemorrhage in patients who received intravenous thrombolysis. Since the exact role

of hypertension on outcome and its time-dependent effect is unknown, we measured systolic and diastolic blood pressure before thrombolysis and multiple times after thrombolysis. We used maximum systolic and diastolic blood pressure after thrombolysis for the analysis.

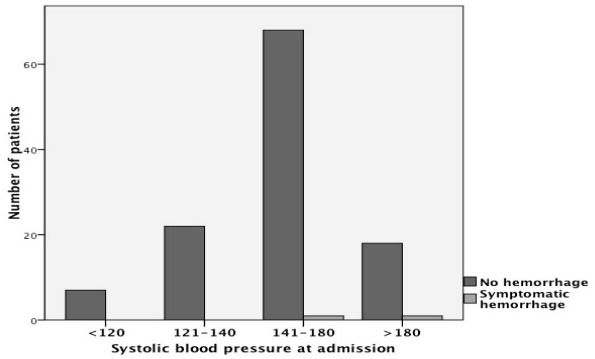

Figure 5. The relationship between number patients who developed symptomatic cerebral hemorrhage following i.v thrombolysis (Data from paper 1I)

Laboratory assessment of acute stroke

All patients admitted with acute stroke undergo a battery of tests that include serum glucose, white blood cells count, platelets count, coagulation profile and electrolytes. Serum glucose is very important because patients with both low and high serum glucose may present with stroke-like symptoms. Platelet count and coagulation profile are important to exclude patients with bleeding risk from receiving thrombolysis. Along with those tests we also collected C-reactive protein (CRP) and serum albumin at the time of admission from all patients admitted ischemic stroke. Paper II, III used those data to analyse its significance on outcome.

Blood Glucose

Previous studies done in thrombolysed and non-thrombolysed ischemic stroke patients have shown that hyperglycemia is associated with poor outcome (Wang, Lim et al. 2000; Williams, Rotich et al. 2002; Baird, Parsons et al. 2003; Alvarez-Sabin, Molina et al. 2004; Leigh, Zaidat et al. 2004). However, there is a hypothesis that hyperglycemia may protect penumbral neuronal tissue from structural damage by improving substrate availability in the early phase. We therefore analyzed the effect of hyperglycemia in the hyperacute phase both before thrombolysis and after

thrombolysis (paper II).

CRP

The role of CRP in primary prevention is debated. However, based on evidence from multiple studies (Ridker, Cushman et al. 1997; Ridker, Hennekens et al. 2000; Rifai and Ridker 2001), AHA recommends use of CRP as a screening tool for primary prevention of coronary aretery disease. The role of CRP in stroke is not as clear as it is in coronary artery disease. Two large studies showed an association between high CRP and risk for future stroke; however the association was not strong enough to use CRP for individual stroke prediction (Rost, Wolf et al. 2001; Bos, Schipper et al. 2006). This difference between coronary artery disease and stroke may be explained by the difference in the etio-pathology of these two vascular diseases. Coronary artery disease is mostly secondary to local atherosclerosis of coronary arteries while stroke is mostly secondary to emboli from a thrombus somewhere else. While this difference may explain how the strength of association between CRP and stroke is not as convincing as in coronary artery disease, the role of high CRP on stroke cannot be discarded since the basic pathology behind most strokes is atherosclerosis somewhere in the vascular system. Chronic inflammation is now known to be a causative factor for atherosclerosis. As an inflammatory marker CRP is considered a potential risk factor for vascular events (Kuller, Tracy et al. 1996; Koenig, Sund et al. 1999; Danesh, Whincup et al. 2000). In the routine clinical practice, CRP is used to rule out acute infections. There is insufficient evidence to use it for risk stratification in ischemic stroke (Di Napoli, Schwaninger et al. 2005). We collected CRP from patients at the time of admission. We assumed that admission CRP level is not affected by stress from the vascular event and therefore represent the chronic inflammatory status of the patient.

Albumin

In routine clinical use serum albumin is used to assess the nutritional status of stroke patients. Patients with low albumin are likely to have a poor nutritional status or poor liver function making them vulnerable to poor outcome after stroke. However, albumin as such was not considered to have a direct biologic effect in the brain. Paper IV showed that high serum albumin is independently associated with better functional and survival outcomes. The biological basis for this epidemiological

association needs to be explained by future experimental research. Temporal variation in albumin occurs during disease state and, interestingly, it follows CRP level (Kaysen, Dubin et al. 2000). It is known from previous studies that CRP level increases following stroke (Di Napoli 2001; Winbeck, Poppert et al. 2002; Emsley, Smith et al. 2003; Pedersen, Waje-Andreassen et al. 2004). Therefore it is likely that albumin level also increases following stroke. Albumin level measured a few days after stroke may not represent the true baseline albumin level. Therefore, in paper IV we used serum albumin at admission to avoid any bias. In clinical practice it is desirable to measure albumin at admission as it helps in prognostication. However, future studies are necessary to determine the benefits of treating hypoalbuminemia.

Neurosonological assessment of acute stroke

Two types of ultrasound technologies are mainly used for cerebral imaging. Transcranial color-coded duplex imaging (TCCD) and transcranial Doppler imaging (TCD). TCCD make use of a combined B-mode imaging along with Doppler imaging while TCD uses blinded Doppler image without the ability to visualize the brain tissue. We used TCD to diagnose intracranial stenosis and to detect microemboli in paper I. The sensitivity of TCD to diagnose intracranial middle cerebral artery stenosis is 93% with a specificity of 96-98% (Demchuk, Christou et al. 2000). While the sensitivity and specificity of combined TCD and TCCD are superior to TCD alone (Chernyshev, Garami et al. 2005), we used TCD alone because of the practical difficulty of performing both the methods during the acute phase of stroke. However, we detected intracranial stenosis in 15% of all the patients who underwent monitoring. This is in correspondence with the prevalence of intracranial stenosis in western population (Hass, Fields et al. 1968; Segura, Serena et al. 2001). We found that the prevalence of microemboli were 50% in patients with intracranial stenosis while micremboli were prevalent in only 8.7% of patients without intracranial stenosis. Figure 6 shows the prevalence of microembolic signals (MES) in patients with and without MES. This shows that the microembolic potential of intracranial stenosis is high as shown in a previous study (Segura, Serena et al. 2001). However, this may not reflect the microembolic potential of asymptomatic chronic intracranial stenosis.

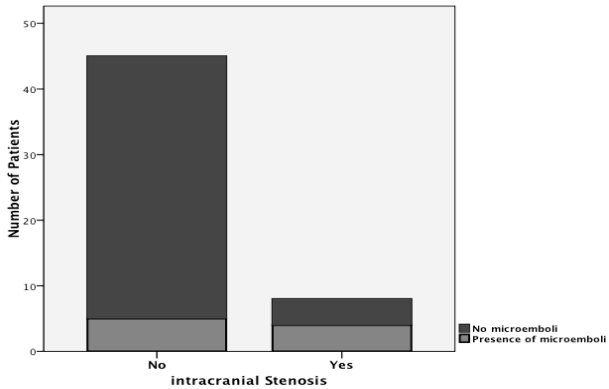

Figure 6. Shows the prevalence of MES in patients detected with intracranial stenosis on TCD (paper I).

The prevalence of microemboli in ischemic stroke varies across different studies from 5.3%-71% (Grosset, Georgiadis et al. 1994; Finocchi, Del Sette et al. 1996; Delcker, Schnell et al. 2000; Lund, Rygh et al. 2000; Serena, Segura et al. 2000; Gucuyener, Uzuner et al. 2001; Kimura, Minematsu et al. 2001; Poppert, Sadikovic et al. 2006). Previous studies show that the prevalence of microemboli is higher with a shorter interval between monitoring and stroke onset (Droste, Dittrich et al. 1999; Kaposzta, Young et al. 1999). Therefore we decided to limit the monitoring to 24 hours from the stroke onset. In our study the prevalence of MES was 19%. A few studies in which microemboli detection was performed in the acute phase following stroke, the prevalence varied from 11-56% (Finocchi, Del Sette et al. 1996; Delcker, Schnell et al. 2000; Serena, Segura et al. 2000; Kimura, Minematsu et al. 2001). Lund et al. performed microemboli monitoring in stroke patients presented within 72 hours after stroke onset in a similar population in the same country (Norway) (Lund, Rygh et al. 2000). The prevalence of microemboli in their study was 26.5%, which is comparable to our study. In our study, monitoring was performed only once after the stroke onset in comparison to two monitoring as performed by Lund et al. We assume that more patients with MES could be detected with multiple monitoring. However, this was not carried out because of the time consuming nature of the monitoring.

Etiological classification of stroke is important in predicting stroke recurrence

(Lovett, Coull et al. 2004). In our study we detected MES only in potentially embolic subgroups (large artery atherosclerosis and cardioembolism). However, we could not associate MES with stroke recurrence because of a lower number of recurrent vascular events than expected. The low number may be related to lack of a systematic follow-up. We used electronic search for re-admission to our hospital for vascular events, which leaves the possibility for missing recurrent vascular events admitted in other hospitals. However, most of the patients with vascular events were re-admitted at our hospital.

Prognosis of stroke

Predicting prognosis after stroke is rather complicated in an individual patient. However, multiple studies have looked into factors that influence outcome after stroke on a group level. A large population based study during the pre-thrombolytic era showed that 58% of patients who survived stroke gained independence and 82% walked independently (Herman, Schmitz et al. 1983). These figures may not represent the outcome today because of newer treatment modalities and identification and treatment of newer factors that influence outcome. A search for all prognostic factors in both the patients who undergo thrombolysis and those who do not undergo thrombolysis are important to identify the patients who might benefit from specific acute interventions and secondary prophylaxis. This may reduce the long-term impact of stroke in the individual patient.

In a pivotal review by Jongbloed, five factors that influence outcome were identified. Those factors were stroke severity, previous stroke, older age, urinary and bowel incontinence and visuo-spatial deficits (Jongbloed 1986). On the other hand Dombovy et al. identified 10 factors that include stroke severity, incontinence, previous stroke, significant cardiovascular disease, advanced age, low pre-morbid intelligence, lack of family support, low socioeconomic class and late admission.

Age

The independent prognostic significance of age is not yet clear (Jongbloed 1986). While most studies show that older patients tend to have a less favorable outcome than the young (Rankin 1957; Adams and Merrett 1961; Kaste and Waltimo

1976; Waltimo, Kaste et al. 1976; Wade, Wood et al. 1985), age does not affect the potential for functional improvement after stroke (Lehmann, DeLateur et al. 1975). Age was a predictor of poor outcome in all the 4 papers in this thesis. However, we have not analyzed if age independently affect improvement in function.

NIHSS

We used NIHSS to assess stroke severity because this is a standard for patients undergoing thrombolytic therapy. In all the 4 papers in which sample size varied from 54 to 498 patients, NIHSS remained an independent predictor of outcome. This further supports previous studies that showed an association between NIHSS and outcome (DeGraba, Hallenbeck et al. 1999; Frankel, Morgenstern et al. 2000). However, we also found out that NIHSS is associated with CRP measured at admission. The association between stroke severity and CRP is rather unclear. It is yet to be proven whether high CRP leads to a higher stroke severity or vice versa. Since we could not prove that CRP is independently associated with stroke outcomes, CRP level most likely reflects the stroke severity.

Temperature

Paper II showed that high temperature after thrombolysis, but not before thrombolysis is associated with poor prognosis. While many animal and clinical studies have shown the deleterious effect of hyperthermia after stroke (Meden, Overgaard et al. 1994; Azzimondi, Bassein et al. 1995; Reith, Jorgensen et al. 1996; Castillo, Davalos et al. 1998; Hajat, Hajat et al. 2000; Suzuki, Bramlett et al. 2004), the results from our study showed that the effect may be time-dependent. This finding prompted us to do anther analysis to study the effect of admission body temperature among patients who underwent thrombolysis (n=111) and who did not undergo thrombolyis (n=139). The analysis showed that hyperthermia was neuroprotective in patients who underwent thrombolyis while hypothermia was neuroprotective in patients who did not undergo thrombolyis (Halvor Naess; Titto Idicula; Nicola Lagallo; Jan Brogger; Ulrike Waje-Andreassen; Lars Thomassen. Inverse relationship of baseline body temperature and outcome between ischemic stroke patients treated and not treated with thrombolysis: The Bergen Stroke Study - Awaiting publication). This indicates that hyperthermia may facilitate the thrombolytic process although it is deletrious to dying neurons. The hypothesis invites future researchs, which may

include assessing the benefit of warming thrombolyic agents prior to intra-arterial thrombolysis.

Blood Pressure

In paper II, we sought to determine how blood pressure influence outcome before and after thrombolysis. The results showed that high systolic blood pressure both before and after thrombolysis were associated with poor outcome. Two patients developed symptomatic hemorrhage in this study and both the patients had high systolic blood pressure at admission (fig. 5). While this may have contributed to poor outcome in patients with high systolic blood pressure, it cannot explain the association. Further studies are needed. Another interesting finding was that we did not find a J-shaped relationship between blood pressure and outcome as shown in some previous studies (Leonardi-Bee, Bath et al. 2002). Low systolic blood pressure even below 120 mm Hg was not a predictor of poor outcome (fig. 7).

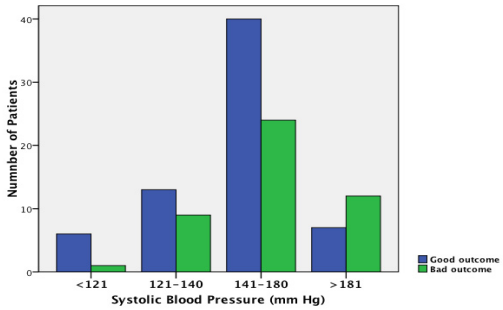

Figure 7. Shows the association between systolic blood pressure at admission and outcome (From the database used in paper II)

Blood Glucose

We found no association between blood glucose before thrombolysis and the outcome. Hyperglycemia immediately after stroke may help penumbral neurons and astrocytes by improving substrate availability and by increasing lactate production that may act as an energy source for dying axons (Nagi, Pfefferkorn et al. 1999; Brown, Tekkok et al. 2003). However, a previous study performed in patients who underwent thrombolysis showed that hyperglycemia hampers the fibrinolytic process.

Unless more studies that support the hypothesis of hyperglycemia-induced penumbral protection, it may be prudent to follow the current guidelines and treat hyperglycemia in stroke patients using insulin both before and after thrombolysis. But we need more studies to further clarify this issue. Hyperglycemia per se is toxic to cells and this is especially true after the 'hyperacute' phase of stroke (Lin, Ginsberg et al. 1998). Apart from that, hyperglycemia also impairs recanalization (Martini and Kent 2007). Multiple studies in the past have shown that hyperglycemia is associated with poor prognosis in stroke patients (Williams, Rotich et al. 2002; Baird, Parsons et al. 2003; Alvarez-Sabin, Molina et al. 2004) which is further confirmed by our finding that hyperglycemia after thrombolysis is deleterious to stroke patients. Our study underlines the importance of monitoring blood glucose and correcting hyperglycemia in stroke patients who underwent thrombolysis.

CRP

As an inflammatory marker, CRP is likely to be a predictor of high stroke incidence and poor outcome in an individual patient who already had a stroke. However, this is yet to be proven. The results from paper IV indicate that CRP is a marker of stroke severity as well as an indicator of poor survival after stroke. The admission CRP was an independent predictor of mortality. This finding opens the possibility for medications that can reduce inflammation such as statins or newer medications that may inhibit CRP. However, we failed to prove any independent association between CRP and short-term functional outcome. These findings supports an "inflammatory hypothesis" which suggests that CRP is an inflammatory marker for the extent of cerebral injury and its complications in contrast to an "atherogenic hypothesis" which suggest that high CRP per se can lead to poor prognosis and high vascular events. In short, our study suggest that measuring CRP at admission in stroke patients will be a good predictor of future mortality and prompt physicians to take measures to reduce vascular risk factors.

Albumin

As an indicator of nutritional status, poor albumin may be considered as an indicator of poor outcome (Yoo, Kim et al. 2008). However, a few animal studies suggest the role of albumin as a neuroprotective agent (Belayev, Busto et al. 1997; Belayev, Pinard et al. 2002). Our study suggests that low serum albumin is associated

with poor functional outcome and poor survival. In other words, high serum albumin is neuroprotective in stroke patients. As of today, scientific community is on an intense search for an effective and safe neuroprotective agent. Most of the agents under trials were proved to be of no benefit (Ferro and Davalos 2006). A few pilot studies show that intravenous infusion of albumin is safe in ischemic stroke patients (Koch, Concha et al. 2004; Palesch, Hill et al. 2006; Shin, Moon et al. 2007). If future studies confirm this finding, this will have clinical implications, i.e, by administering albumin as a neuroprotective agent. Our findings lend support to this possibility.

Microemboli

Our results showed that there is a moderate prevalence of microemboli (18.5%) during the first 24 hours after stroke onset. Almost all patients with microemboli belonged to embolic etiology (cardioembolic or large-artery atherosclerosis). Microembolic detection may thus help us to better classify the etiological diagnosis of stroke. The study, however, failed to show any association between microemboli and outcomes. Further studies are needed to clarify conflicting data on the prognostic implications of MES.

Conclusions

The first 24 hours after stroke onset is a critical phase in which the potential for neurological improvement are maximal. The process of neuronal death starts at the onset of thrombotic occlusion and may continue for hours or possibly days. Once dead, neurons cannot be re-generated. Therefore, reversal of neuronal damage is extremly important during the very early hours after the onset of stroke. This is true for both patients who undergo thrombolysis and those who do not. The factors that are detrimental in the process of neuronal death are not completely understood. We aimed to delineate the role of certain physiological and laboratory parameters that influence outcome during the first 24 hours after stroke.

Measurement of physiological parameters like body temperature and blood pressure are very important during the first 24 hours. These factors exert a time-dependent effect on outcome especially in thrombolysed patients. While factors like hyperthermia and hyperglycemia before thrombolyis did not have a negative

influence on outcome, they were deleterious after the thrombolysis. This finding is strongly suggestive of performing a rigorous monitoring and correction of deranged physiological parameters during and immediately after thrombolysis.

The routine measurement of CRP and serum albumin is not recommended in the current stroke guidelines. However, our study shows that they may help prognostication. Moreover, correction of low albumin with intravenous albumin therapy may have a therapeutic impact, which needs to be further confirmed with randomized trials. A systematic and uniform way of collecting data from stroke patients admitted to our unit will make the results more reliable and enable us to perform further analysis with a larger sample. Our preliminary study thereby gives a foundation for further research.

Neurosonology is being increasingly used in stroke patients because of the ease of conducting the test and the non-invasive nature of the procedure. Ultrasound-guided detection of an intracranial or extracranial stenosis has therapeutic implication whereas microemboli detection helps better classify the stroke and identify the stroke etiology. A better etiological classification will certainly improve clinical studies and a thorough etiological work-up may have some clinical implication in certain situations like an unstable carotid plaque – a potential source of emboli. The presence of microemboli per se may not have any prognostic implications as shown in our study. However it is yet to be proven whether interventions to abort microemboli help to prevent future vascular events and cerebral injury. Future studies are invited.

Acute stroke is a complex disease. A complex combination of accurate clinical examination, morphological imaging of brain parenchyma, arterial imaging of atherosclerosis, assessment of hemodynamics, detection of circulating microemboli, careful assessment of physiologic parameters, and blood tests are necessary to classify the etiology of stroke and to provide appropriate treatment. Our study shows that each of these parameters has their own significance in predicting prognosis after stroke.

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