INTRODUCTION

• Stroke has become a major challenge for health policy and for medicine and is now the second most common cause of death world-wide.

• A continuing rise of incidence rates in the world has made stroke a global problem.
INTRODUCTION

- Childhood stroke is a neglected area, with both professionals and the general public lacking awareness of the problem and its potential consequences.
- Stroke affects 6-13/100,000 each year in different nations, i.e.: more than twice of childhood brain tumor
INTRODUCTION

• Stroke is one of the top ten causes of childhood death allover the world.
• Many children who have a stroke have another medical condition (such as a cardiac disorder or sickle cell disease).
• Those children are vulnerable to adverse neurodevelopmental effects
DEFINITION

• Stroke: focal neurological deficit with a vascular basis lasting > 24 hours.

• Transient ischemic attack (TIA): similar episode for a shorter period of time
INCIDENCE

- Incidence is between 1.2 and 2.52/100,000 children / year (in pre CT era)\(^1\).
- Incidence is 13/100,000 children / year (7.91/100,000 for ischemic stroke and 5.11/100,000 hemorrhagic stroke (in CT era)\(^2\).

1-Schoenberg, Hellinger & Schoenberg, 1978
2-(Giroud et al., 1995).
In separate research, the rates of stroke for full term neonates, a group often excluded from other studies, has been estimated at approximately 10 in 100,000\(^3\).

3-Koelfen, Freund, & Varnholt, 1995
INCIDENCE DISTRIBUTION IN ADULTS AND CHILDREN

<table>
<thead>
<tr>
<th>Type</th>
<th>Adults</th>
<th>Children</th>
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<tbody>
<tr>
<td>Hemorrhagic</td>
<td>80</td>
<td>40</td>
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<tr>
<td>Ischemic</td>
<td>40</td>
<td>60</td>
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ETIOLOGY OF ISCHEMIC STROKE

• Cardiac disease
  – Congenital heart disease
  – Infective endocarditis
  – Valvular disease
  – Arrhythmias

• Hematologic
  – Sickle cell disease
  – Inherited coagulopathy
  – Myeloproliferative disorders

• Primary vasculopathy
  – Fibromuscular dysplasia
  – Infections
  – Takayasu arteritis
  – SLE and other autoimmune diseases
  – Infectious vasculitis

• Trauma
  – Blunt trauma to posterior pharynx
  – Cervical spine rotation or dislocation
ETIOLOGY OF ISCHEMIC STROKE

• **Metabolic**
  – Homocystinuria
  – MELAS

• **Drugs**
  – “recreational” e.g. cocaine, Heroin
  – Sympathomimetics
  – L-asparaginase

• **Surgical intervention**
  – Cardiac surgery
  – Cardiac catheterization
  – Cerebral angiography

• **Neurocutaneous syndromes**
  – Neurofibromatosis
  – Tuberous sclerosis
  – Sturge Weber
ETIOLOGY OF HEMORRHAGIC STROKE

- Vascular malformations
  - AVM
  - Capillary telangiectasis
- Aneurysms
  - Saccular
  - Infective
- Hypertension
- Bleeding diathesis
  - Factor deficiencies
  - Thrombocytopenia
  - DIC
  - Leukemia
  - Polycythemias
  - Anticoagulant, thrombolytic therapy
- Vasculitis
PATHOPHYSIOLOGY

- Cerebral embolism
- Arterial thrombosis
- Venous thrombosis
- Intraparenchymal hemorrhage
- Lacunar infarction
- Subarachnoid hemorrhage

How
PATHOPHYSIOLOGIC MECHANISMS

Penumbra
(blood supply 20 – 50 mL/100 g/min)

Core
(blood supply 0 – 12 mL/100 g/min)

**Core**: central area where ischemia is severe & infarction develops rapidly

**Penumbra**: marginally perfused area surrounding the core which has the capacity to recover should perfusion be restored promptly
Complete interruption of cerebral blood flow

- Suppression of electrical activity within 12–15 sec
- Inhibition of trans-synaptic excitation after 2-4 min
- Inhibition of electrical excitability after 4-6 min
- Breakdown of metabolism shortly thereafter
Neurons and Glia remain alive but functionless for as long as 30 min before cellular death starts to occur.

The possibility that restoration of flow during the interval between loss of neuron activity and tissue death might restore function is the basis for therapy of the evolving cerebral infarction.
The Molecular Events Initiated in Brain Tissue by Acute Cerebral Ischemia
FACTORS INFLUENCING THE SIZE OF ISCHEMIC INFARCTION

- Time course of involvement
- Collateral blood supply
- Perfusion pressure (MAP)
- Tissue oxygen supply
- Glucose supply
FACTORS INFLUENCING THE SIZE OF ISCHEMIC INFARCTION

- Accumulation of lactic acid, neurotransmitters, free radicals, superoxides
- Local tissue temperature, and Inflammation.
- Development of cerebral edema
- Venous occlusion
CLINICAL PRESENTATION

• Hemiparesis (91%)
• Hemisensory signs
• Visual field defects
• Gaze palsy or head turning $\Rightarrow$ large supratentorial infarct
• Headache $\Rightarrow$ arterial dissection, cerebral venous thrombosis
• Seizures $\Rightarrow$ cerebral venous thrombosis, & neonatal stroke.
• $\downarrow$ LOC $\Rightarrow$ cerebral hemorrhage, large MCA territory infarct, posterior fossa stroke
CLINICAL PRESENTATION

• Embolism
  – **Onset** Dramatic
  – Sudden loss of function
  – Symptoms depend on location & size of occluded vessel
  – Most often associated with cardiac disease

• Arterial Thrombosis
  – **Onset** Subacute
  – Prodromal symptoms,
  – TIAs,
  – Stuttering course
CLINICAL PRESENTATION

- **Venous thrombosis**
  - **Onset** Variable
  - Seizures
  - ↑ ICP
  - Altered mental status
  - Focal neurologic signs

- **Intraparenchymal hemorrhage**
  - **Onset** Acute, of headache, vomiting, deterioration of function
  - Sometimes subtle findings
CLINICAL PRESENTATION IN NEONATAL STROKE

• Seizures – most common
• Hypotonia, lethargy, and apnea
• Can be diagnosed retrospectively in patients who are failing to reach milestones or have hemiparesis
DIFFERENTIAL DIAGNOSIS

- Tumors
- Trauma
- CNS infection
- Demyelinating conditions
- Todd’s paresis
- Migraine
EVALUATION FOR SUSPECTED STROKE

• **Neuroimaging**
  – MRI and MRA
  – **CT** scan

• **For those with hemorrhage**
  – Basic coagulation studies and platelet count
  – Conventional angiography if no bleeding diathesis
EVALUATION FOR SUSPECTED STROKE

- For those with an infarct in a vascular distribution
  - CBC, ESR
  - Iron, folate, Hb electrophoresis
  - Protein S, protein C
  - AT III, heparin cofactor II, plasminogen, factor VIII, factor XII, lupus anticoagulant
  - Anticardiolipin antibodies
  - Factor V Leiden & activated protein C resistance
  - Prothrombin-G 20210 gene
EVALUATION FOR SUSPECTED STROKE

• For those with an infarct in a vascular distribution
  – Total homocysteine (& thermolabile MTHFR gene, serum folate, B6, B12)
  – Fasting cholesterol, triglycerides, Lp(a) lipoprotein
  – Infection screen- Mycoplasma, Chlamydia, Helicobacter, Borrelia titers
  – Serum and CSF titers to varicella zoster
  – ECG, echocardiography, x-ray chest
EVALUATION FOR SUSPECTED STROKE

• For those with infarction in the vertebrobasilar territory (in addition)
  – X-ray C-spine in flexion and extension

• For those with infarction not in a typical vascular distribution
  – CSF lactate
  – Plasma ammonia and amino acids
  – Urine organic acids
  – Echocardiography
  – Antiphospholipid antibodies
NEUROIMAGING

Imaging of the brain
- Is it a stroke?
- Ischemic infarct or hemorrhage?
- Where is it?
- How large is it?
- How old is it?

Imaging of the vessels
- Is there blockage?
- Where?
- How severe?
- Pathology?
- Other vascular lesions?
NEUROIMAGING

- **Anatomical**
  - CT Scanning
  - MRI
  - Duplex and Transcranial Doppler
  - MRA
  - Conventional angiography

- **Functional**
  - Functional MRI
  - Studies of blood flow and metabolism
  - MR Spect
  - PET
TREATMENT OF ACUTE STROKE

GOALS

• To achieve rapid restoration & maintenance of blood supply to the ischemic areas
• Minimize brain damage
• Prevention/Treatment of acute complications
• Supportive care
• iv t-PA for carefully selected patients who can be treated within 3 hours of onset of ischemic stroke
• Odds of death or total dependency at final follow up decreased by 44% compared with placebo (95% C.I. 18-48)
• Odds ratio of symptomatic intracranial hemorrhage 3.1 (95% C.I. 2.3-4.2), fatal intracranial hemorrhage 3.6 (95% C.I. 2.3-5.7)
IV THROMBOLYTIC THERAPY IN CHILDREN

- Pooled literature analysis of 203 children treated with thrombolytics for non-cerebral thrombotic complications: thrombus cleared in 80%, minor bleeding in 54%, ICH in 1 child
- 29 children treated with t-PA at Toronto’s Hospital for Sick Children: clot dissolved in 79%, almost 25% had bleeding which required transfusion
INTRAARTERIAL THROMBOLYTIC THERAPY

- Option for selected patients with major ischemic stroke due to occlusion of MCA within 6 hours of onset

- Not approved by FDA
ANTITHROMBOTIC THERAPY

• Start within 48 hours after ischemic stroke unless thrombolytic therapy is planned
• Aspirin 2- 3 mg/kg/day
• Decreases odds of recurrent stroke during treatment period by 13% (95% C.I. 3-21%)
• Decreases odds of death or dependency at final follow up by 5% (95% C.I. 1-9%)
ANTICOAGULANTS

• Routine use, of heparin, low molecular weight heparin or heparinoids, is NOT recommended after ischemic stroke in children
• Increased risk of hemorrhagic transformation of infarct
NEUROPROTECTIVE STRATEGIES

• Includes calcium channel blockers, glutamate antagonists, barbiturates, free radical scavengers, etc.

• Many are used currently, but none is FDA approved.
SUPPORTIVE CARE

- Maintain normal temperature
- Maintain oxygen saturations > 95%
- Maintain blood glucose < 300 mg/dl
- Correct hypoglycemia
- Treatment of hypertension controversial
- Plan rehabilitation
- Nutrition and assessment of swallowing
- Early mobilization to decrease risk of aspiration pneumonia, venous thromboembolism, pressure sores and contractures
PREDICTORS OF POOR OUTCOME

CLINICAL FEATURES
- Decreased LOC
- Temperature > 38.5°C
- Severe BP elevation
- Large vessel disease

BASELINE LAB DATA
- Plasma glutamate > 200 µmol / L
- C-reactive protein > 10.1 mg / L¹
- Serum glucose < 7 mmol / L (no t-PA), > 6.6 mmol / L predicts ICH (t-PA)²
- Platelet count < 150,000 / µL predicts ICH

¹- Kitchener et al., 2005
²- Toronto Pediatric Stroke Group, 2006
PREDICTORS OF POOR OUTCOME

RADIOLOGIC INVESTIGATIONS

- CT scan: hyperdense MCA sign
- > 33% MCA territory density
- MCA + ACA, PCA or AchA territory hypodensity
- Transcranial Doppler: complete occlusion, no flow
- Carotid ultrasound: stenosis or occlusion
- SPECT: absent rCBF
- Angiography: ICA “T”, proximal MCA or BA occlusion, no collaterals
- MRI: DWI abnormality large, PWI abnormality large
- MRA: MCA flow void

3- Kitchener et al., 2005
OUTCOME

• Survival in first month:
  – after ischemic stroke: 85-95%
  – after hemorrhagic stroke: 60-80%

• Prognosis better in children than in adults

• Residual deficit in \( \geq \) 75% cases

• Disability: hemiparesis, learning disabilities, mental retardation, seizures, movement disorders
PREVENTION OF RECURRENCE

• Ischemic stroke recurs in 6-20% of all children and in > 60% of children with sickle cell disease

• For Sickle Cell Disease
  Regular transfusions to keep HbS < 30%
  Consider bone marrow transplantation
  Consider hydroxyurea if regular blood transfusions not feasible
PREVENTION OF RECURRENCE

• For Moyamoya
  Consider revascularization

• For homozygotes for the thermolabile MTHFR gene
  Vitamin B complex supplementation
PREVENTION OF RECURRENCE

- For those with extracranial arterial thrombosis and/or stenosis: Consider anticoagulation

- For those with prothrombotic disorders
  Consider anticoagulation

- For others with cerebrovascular disease
  Low dose aspirin (1-3 mg/ kg/ day)