CRYPTOGENIC STROKE

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I have no financial relationships or other conflict of interests to disclose, and I will not discuss off label use and/or investigational use in my presentation.
OBJECTIVES

- Describe normal cerebral circulation
- Discuss incidence and types of strokes
- Define cryptogenic stroke
- List the main causes of ischemic strokes
- Describe available tests used to determine stroke etiology
- Discuss long term solutions for determining stroke etiology and initiate early treatment to prevent secondary stroke
NORMAL CEREBRAL ANATOMY
BRAIN ANATOMY
FUNCTIONAL CORTEX
NORMAL CEREBRAL CIRCULATION
MAJOR VESSELS
NORMAL CEREBRAL CIRCULATION
NORMAL CEREBRAL CIRCULATION
Carotid arteries and the basilar artery feed into the Circle of Willis

Circle creates a “backup” system

Communicating arteries connect the major brain arteries

Blood can flow both ways and shift blood from other arteries to compensate for blockages if necessary
BLOOD SUPPLY TO THE CNS
TYPES OF STROKE

Ischemic versus Hemorrhagic
Embolic versus Thrombotic
STROKE - DISRUPTION OF NORMAL BLOOD FLOW TO THE BRAIN
ISCHEMIC VERSUS HEMORRHAGIC STROKES
ISCHEMIC
ISCHEMIC
THROMBOSIS VERSUS EMBOLISM IN ISCHEMIC STROKES
THROMBOSIS VERSUS EMBOLISM IN ISCHEMIC STROKES
THROMBOSIS VERSUS EMBOLISM IN ISCHEMIC STROKES
CRYTOPGENIC STROKE

Defined!

Why it’s important to solve the mystery!
Cryptogenic stroke (CS) is defined as cerebral ischemia of obscure or unknown origin. The cause of CS remains undetermined because the event is transitory or reversible, investigations did not look for all possible causes, or because some causes truly remain unknown. One third of the ischemic strokes is cryptogenic.

Management of cryptogenic stroke. - NCBI


CRYPTOGENIC STROKE
(AKA: EMBOLIC STROKE OF UNKNOWN SOURCE [ESUS])
IDENTIFIABLE CAUSES OF ISCHEMIC STROKE

Cardiac
Large Vessel
Small Vessel
Hematologic
# Causes of Ischemic Stroke

## Causes of Stroke

### Cardiac Source
- Arrhythmias
- Valve disease
- Dilated cardiomyopathy
- Recent myocardial infarction
- Paradoxical emboli
- Aorta

### Large-Vessel Disorders
- Atherosclerosis or dissection in the carotid or vertebrobasilar system

### Small-Vessel Occlusive Disease
- Hypertension-induced disease
- Isolated central nervous system angitis
- Systemic lupus erythematosus

### Hematologic Disorders
- Polycythemia
- Thrombocytosis
- Severe leukocytosis (acute leukemia)
- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden mutation
- Hypercoagulable state
CAUSES OF ISCHEMIC STROKE
CARDIAC CAUSES

Atrial Fibrillation
Valvular Heart Defects
Structural Defect
Ventricular Thrombus
Atrial Fibrillation Is the Most Common Cause of Cardioembolic Ischemic Stroke

Cardiac Diseases Leading to Cardioembolic Events

- Atrial fibrillation: 50%
- Ventricular thrombus: 15%
- Valvular heart disease: 15%
- Structural heart defects or tumors: 20%
CARDIOEMBOLIC STROKE: ATRIAL FIBRILLATION
VALVULAR HEART DISEASE
PATENT FORAMEN OVALE/ATRIAL SEPTAL DEFECT
VENTRICULAR THROMBUS
LARGE ARTERY ATHEROSCLEROSIS
LARGE ARTERY ATHEROSCLEROSIS
LARGE ARTERY ATHEROSCLEROSIS
SMALL ARTERY/LACUNAR STROKES
ISCHEMIC STROKE:
Small-Vessel Stroke

-lacunar infarction: infarction following atherothrombotic or lipohyalinotic occlusion a small artery (30-300 micrometer) in the brain
-account for 20% of all strokes

PATHOPHYSIOLOGY:
-arteries that give rise to 30-300 micrometer branches that penetrate the cerebrum or brainstem:
  -MCA
  -circle of Willis
  -anterior and posterior communicating
  -basilar
  -vertebral
LACUNAR STROKES
Lacunar syndromes;

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Signs/Symptoms</th>
<th>Localization</th>
<th>Vascular supply</th>
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</table>
| Pure motor    | Contralesional hemiparesis | - Internal capsule  
- posterior limb  
- Corona radiata  
- Basis pontis          | - Lenticulostriate branches of the MCA or  
- perforating arteries from basilar artery |
| Pure sensory  | Contralesional hemisensory loss | - VPL nucleus of thalamus                             | - Lenticulostriate branches of MCA  
- Small thalamoperforators of PCA |
| Sensorimotor  | Contralesional weakness and numbess | - Thalamus and adjacent posterior limb of internal capsule | - Lenticulostriate branches of MCA |
HYPERCOAGULATION AND STROKE
HYPERCOAGULABLE STATE/THROMBOSIS
HYPERCOAGULABLE STATES/THROMBOSIS
Box 1: Conditions and coagulation defects associated with thrombosis\textsuperscript{1,3}

**Arterial thrombosis\textsuperscript{*}**
- Antiphospholipid antibody syndrome, primary or secondary
- Hyperhomocysteinemia
- Prothrombin G20210A mutation
- Antithrombin deficiency (suggested by “heparin resistance”)
- Protein S deficiency
- Vasculitides (giant cell arteritis, Takayasu’s arteritis)

**Venous thrombosis\textsuperscript{†}**
- Factor V Leiden (resistance to activated protein C) (< 40%)
- Antithrombin deficiency (3%-8%)
- Protein C or S deficiency (5%-10%)
- Prothrombin G20210A mutation (6%-18%)
- Lupus anticoagulant or antiphospholipid antibody syndrome (5%-10%)
- Hyperhomocysteinemia (10%-20%)

\textsuperscript{*}The conditions listed are uncommon causes of arterial thrombosis compared with the most prevalent condition, atherosclerotic disease.
\textsuperscript{†}Percentages indicate prevalence among all cases of venous thrombosis.
<table>
<thead>
<tr>
<th>Group 1 disorders (hereditary deficiencies of coagulation factor inhibitors). Many patients with these disorders will have had venous thrombosis by age 60 years.</th>
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<tbody>
<tr>
<td>Protein C deficiency</td>
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<td>Protein S deficiency</td>
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<tr>
<td>Antithrombin deficiency</td>
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<tr>
<td>Group 2 disorders (hereditary disorders associated with increases in the levels or function of the coagulation factors). These disorders are associated with a lower risk for thrombosis than the group 1 disorders, and most affected individuals will not have had thrombosis by age 60 years.</td>
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<td>Activated protein C resistance and factor V Leiden</td>
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<td>Prothrombin regulatory sequence mutation</td>
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<td>Elevated levels of factors VIII, IX, and XI</td>
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<td>Elevated levels of lipoprotein(a)*</td>
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<td>Dysfibrinogenemia</td>
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<td>Other disorders</td>
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<tr>
<td>Hyperhomocysteinemia</td>
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<td>Plasminogen deficiency</td>
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<tr>
<td>Increased levels of thrombin-activatable fibrinolysis inhibitor</td>
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DETERMINING CAUSES

Inpatient testing
Long term testing
Lab tests for diagnostic of hyper coagulation state

- Factor (V) leiden
- Antithrombin III
- Prothrombin 20210
- Protein C
- Protein S
- Protein Z
- Homocysteine
- Specific platelet protein and increase of it’s metabolism
- Decrease of fibrinolytic action
- ACLA, LACT, dRWVT
- D-dimmer, PTT
ECHOCARDIOGRAM – TRANSESOPHAGEAL/TRANSTHORACIC
DETERMINING CAUSES/BEGINNING TREATMENT
EKG MONITORING: IN PATIENT OPTIONS
LONG TERM EKG MONITORING OPTIONS
LONG TERM EKG MONITORING OPTIONS
IMPLANTABLE LOOP RECORDER

- The implantable loop recorder or insertable loop recorder (ILR) is a subcutaneous monitoring device for the detection of cardiac arrhythmias that stores events when the device is activated automatically according to programmed criteria.
- This device can be useful in the evaluation of palpitations or syncope of undetermined etiology, particularly when symptoms are infrequent (e.g., less than once per month).
- In such patients, conventional noninvasive testing is often negative or inconclusive.
“An implantable loop recorder is a small electrical device that is able to record the heart activity.

“It is about the size of a computer USB and sits underneath the skin. There are no wires to the heart. It allows continuous recording of the heart’s activity so that we can diagnose arrhythmias.”
Embolic Strokes of Undetermined Source (ESUS): The Case for a New Clinical Construct

- Prior studies showed no benefit due to
  - Less well defined patient population
  - Coumadin with increased bleeding risk

- New clinical trial to include
  - ESUS platform
  - New generation oral anticoagulant
  - May provide a valid treatment options for this group of patients

PROPHYLACTIC TREATMENT?
PROPHYLACTIC TREATMENT?
- Critical to determine cause of primary stroke
- Multiple reasons for strokes to occur
- We are unable to currently have a definitive diagnosis in up to 30% of ischemic strokes
- New tools available now to assist in monitoring for atrial fibrillation that may help identify more paroxysmal atrial fibrillation further reducing the incidence of secondary stroke
- There is on-going research on treatment options for ESUS
- New guidelines for the treatment of stroke may be available soon!
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