Hereditary metabolic causes of stroke and pseudo-stroke

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Introduction

Cerebrovascular disorder: a focal cerebral injury with an underlying vascular basis
- Ischemic stroke (arterial or venous): a vascular insufficiency → a focal cerebral infarction → a focal neurologic deficit > 1 hour.
- Hemorrhagic stroke
  → parenchymal hemorrhage with a focal neurologic deficit
  → subarachnoid hemorrhage, often without focal deficit

Stroke-like episode: a focal cerebral disturbance
- not primarily due to a vascular insufficiency
- a focal neurologic deficit that is persistent but can recover
- metabolic decompensation of a focal brain region
- neurological deficit occurs episodically or a progressive course
- Stuttering onset with a migraine-like prodrom lasting several hours.

Cardio-embolic stroke

Metabolic disorders → cardiomyopathy and poor ventricular function.
- Glycogen storage diseases: Pompe disease and Danon disease (an X-linked dominant condition with LAMP2 mutations)
- Mitochondrial cytopathy
- Fabry disease

IEM → vascular insufficiency
- Homocystinuria
- Fabry disease
- CDG syndrome

Classical Homocystinuria


Risk
- 25% by age 16
- 50% by age 29

Classical Homocystinuria

- In young patients
- Cerebral sinovenous thrombosis or arterial ischemic stroke
- Without systemic signs
- Pitfall of neonatal screening
- Biochemical investigations
  - Total homocysteine in plasma
  - Amino-acids in plasma: ↑ homocystine, methionine
  - Organic acids in urines: methylmalonic acid
  - Molecular analysis

Introduction

Cardio-embolic stroke

IEM → vascular insufficiency

Homocystinuria, MTHFR deficit and cobalamin deficiencies

Fabry disease

CDG syndrome

Fabry disease

Natural history: stroke
6.9% males
6.3% females
< the age of 30 years: 20%

The mean age at first stroke
39.8 years for males
45.7 years for females

86.8%: ischemic strokes
13.2%: hemorrhagic strokes

Fabry disease

- 1.2% of cryptogenic strokes in patients < 55 years in the absence of other clinical manifestations.
- More commonly affects the posterior circulation.

Pathophysiology
- ↑ prevalence of traditional stroke risk factors: cardiac valvular disease, left ventricular hypertrophy, cardiac arrhythmia, hypertension.
- ↑ Gb3 in endothelial and vascular smooth muscle cells → progressive stenosis and occlusion of small arterial vessels → dilatation of the large vessels, resulting in dolichoectatic changes and flow stagnation.
- Abnormalities in cerebral blood flow velocity.
- A prothrombotic state.
- Increased production of reactive oxygen species.

Diagnosis
- Direct measurement of α-gal activity in leukocytes or plasma.
- Women: molecular analysis.

Treatment
- Enzyme replacement therapy.
- Prevention of stroke.

Introduction

Cardioembolic stroke

IEM → vascular insufficiency

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Fabry disease

CDG syndrome

CDG: congenital defects of glycosylation


- 14 cases of thrombosis: 50% arterial and 50% venous thrombosis
- From a few days to adulthood with a mean age of 4.6 years.
- 14 cases of hemorrhage.

Thromboses: venous or arterial.

- Permanent state of coagulation activation: elevated D-dimer.
- Deep venous thrombosis, common iliac artery thrombosis, abdominal aortic thrombosis, a thrombosis of the auriculum, a bilateral iliac venous thrombosis, sinuses cavernous thrombosis.
- Ischemic cerebral vascular accidents.

Central and umbilical catheters, immobilization, infections.

Both hemorrhage and thrombosis: same patients.
**CDG: congenital defects of glycosylation**

Stroke-like episode
- The average age of onset: 4–5 years
- Sudden drowsiness or coma + neurological impairment: hemiparesia, aphasia, cortical blindness, partial or generalized seizures
- Transient symptoms: - several hours to months

Imbalance of anticoagulation and procoagulation factors
Prophylaxis with low doses of aspirin after a first arterial thrombosis

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**Clinical case**

- 28 year-old girl admitted for neurological evaluation of acquired speech difficulties, right lateral homonymous hemianopsia.

**History**
- Deafness (age of 14 years) treated with hearing aids
- 03/2014: Severe headache; Status epilepticus: Levetiracetam
- 05/2014: Severe headache, vomiting, photophobia; Severe left lateral homonymous hemianopsia.
- 06/2014: Hospitalisation in psychiatry
- 04/2015: Severe headache, vomiting, photophobia; Severe right lateral homonymous hemianopsia

**Table 1**

Initial manifestations of MELAS syndrome.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Manifestations</th>
</tr>
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<tbody>
<tr>
<td>&gt;25%</td>
<td>Seizure</td>
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<tr>
<td></td>
<td>Recurrent headaches</td>
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<tr>
<td></td>
<td>Stroke-like episode</td>
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<tr>
<td></td>
<td>Cortical vision loss</td>
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<tr>
<td></td>
<td>Muscle weakness</td>
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<tr>
<td></td>
<td>Recurrent vomiting</td>
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<tr>
<td></td>
<td>Short stature</td>
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<tr>
<td>10–24%</td>
<td>Altered consciousness</td>
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<tr>
<td></td>
<td>Impaired mentation</td>
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<tr>
<td></td>
<td>Hearing impairment</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
</tr>
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<td></td>
<td>Developmental delay</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>Fever</td>
</tr>
</tbody>
</table>

**Clinical case**

- Coagulation testing: normal results
- Heart investigations: left ventricular hypertrophy
- CSF analysis: lactate: 3.5 mmol/l
- Genetic investigations: m.3243A>G mutation in the MT-TL1 gene of mitochondrial DNA

⇒ MELAS

**MELAS**

- Evaluation of multi-organ involvement
- Management of complications:
  - Cochlear implants
  - Anticonvulsant therapy and standard analgesics
  - Cardiac, endocrine follow up
  - Exercise
- L-Arginine therapy
  - IV L-arginine (0.5 g/kg for children/10 g/m2 body surface area for adults)
  - A similar daily dose orally in 3 divided doses during the interictal phase
- CoQ10
- Creatine
- Medications to avoid:
  - Valproic acid
  - Dichloroacetate
  - Aminoglycosides, linezolid, and alcohol
  - Cigarette smoke
Introduction

Cardio-embolic stroke

IEM \rightarrow vascular insufficiency

Homocystinuria, MTHFR deficit and cobalamin deficiencies

Fabry disease

CDG syndrome

IEM \rightarrow stroke-like episodes

CDG syndrome

MELAS syndrome / POLG mutations

Clinical case

18 months-old girl

- Hemicranial headache
- Neuropathic manifestations

Brain MRI:

- Amino-acids: high level of glutamine
- Orotic acid: high level in the urines

OTC deficiency

- Anemia: hemaphagotic syndrome

Clinical case

6 years-old girl

Cardiological evaluation: normal anatomy

Hematological evaluation:

- LDH 648 U/I
- Hemoglobin 11.1 g/dl
- White cells 2.7x10³/µL
- Neutrophils 0.95x10³/µL
- Platelets 230x10³/µL

Bone marrow aspiration: hemophagocytic syndrome

Kidney ultrasound + Doppler: normal
Clinical case

6 years-old girl

- Revascularization with burr holes surgery over each hemisphere, in 2 staged procedure at an interval of 3 months
- Metabolic investigations
  - Blood proteins level: 5 mg/dl (nl 6.1-7.9)
  - Liver and kidney functions: normal values
  - Ammonia: 81-100 µg/dl (nl < 125)
  - Lactic acid: 0.9 mmol/l
  - Organic acids in urine: normal values
  - Amino-acids in urine: increased levels of all amino-acids

Clinical case

6 years-old girl: Protein load up to 1 g/kg/day

Amino-acids in plasma

- Glutamine: 1205 µmol/L → 4201
  - 250 - 850
- Ornithine: 24 µmol/L → 7
  - 24 – 104
- Lysine: 28 µmol/L → 30
  - 60 – 230
- Arginine: 7 µmol/L → 0
  - 32 – 117

Amino-acids in urine

- Ornithine: 98 mmol/mol creat
  - < 7
- Lysine: 1185 mmol/mol creat
  - 68
- Arginine: 526 mmol/mol creat
  - < 7

Orotic acid in urines: 6.9 mmol/mol creat
  - < 3,3

Moyamoya syndrome associated with metabolic disorders

- Glycogen storage disease (type Ia) (Egashira. J Neurosurg Pediatr 2011)
- Primary oxalosis (Lammie. Cerebrovasc Dis. 1998)
- Homocystinuria (van Diemen. Neuropediatrics 1990)

Stroke and stroke-like episodes

Metabolic diseases

Genetic counseling

Treatable disorders

Quality of life

Consanguineous parents
- Severe moyamoya syndrome
- Hemophagocytosis syndrome
- Failure to thrive

Protein-restricted diet (15 g protein/day) + citrulline

Lysinuric protein intolerance