INTRACEREBRAL HAEMORRHAGE: what is the cause?

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Director, Lille haemorrhagic stroke research program

Lille University Hospital
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## DISCLOSURES

### Stocks
None

### Drug trials (< 5 years)
- **Lundbeck** 2011 Dias-3 (investigator)
- **Brainsgate** 2012 Impact-24 (investigator)
- **Sanofi-Aventis** 2012 ASY (investigator)
- **Pierre Fabre** 2013 LIFE (investigator)
- **Pfizer** 2014 A9951024 (PI France)
- **Astra-Zeneca** 2015 Socrates (investigator)

### Board (<5 years)
- Bayer – Daiichi Sankyo - Medtronic

### Speaker honoraria (<2 years)
None

### Travels (<1 year)
None

No personal funding - Funding to Research account (Lille University Hospital) or ADRINORD.

CC March 2016
~3.4 million new ICrH worldwide in 2013

Neuroepidemiology 2015;45:161-76
**Risk of ICH increases with age**

Overall ICH incidence has been stable for the last 30 years

Incidence rate
- 6.2/100,000/year in females
- 9.1/100,000/year in males

Mean age at onset
  - Impact of primary prevention

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Van Asch C. Lancet Neurol 2010

Profiles of patients are changing
Underlying vessel disease are changing

- 50% decrease in <60y
- 80% increase in ≥75 & increased antithrombotic use
- Some bleeding prone vasculopathies are more likely to bleed when antithrombotics are used, especially in lobar ICH

FORGET ‘PRIMARY’

Trauma

Spontaneous

- With malformation
  - Risk factors?
    - Hypertension
    - Hypocholesterolemia
    - Alcohol
  - Precipitating factors?
    - Antiplatelets
    - Warfarin

- Without malformation
<table>
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<tr>
<th>Cause*</th>
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*In descending order of frequency, although haemorrhage.

FORGET ‘PRIMARY’
2 MOST FREQUENT CAUSES

DEEP

- «Deep perforating vasculopathy»

VERSUS

LOBAR

- Cerebral Amyloid Angiopathy

Thal JNEN 2003

Courtesy De Reuck J
**Deep perforating vasculopathy**

- Frequent cause of ICH
- Search for markers of small-vessel disease
  - Leukoaraiosis
  - Lacunes
  - Other organ damage such as retina, heart, kidney?
**Deep perforating vasculopathy**

- Woman, 68 years old
- HTN for 20 years
- Treatment at home: ACE inhibitors, diuretics
DEEP PERFORATING VASCULOPATHY

- Woman, 60 years old
- HTN for 15 years, diabetes for 5 years
- Treatment at home: calcium blockers
MRI Day 3

T2* GRE

FLAIR
Deep perforating vasculopathy

- Frequent cause of ICH
- Search for markers of small-vessel disease
  - Leukoaraiosis
  - Lacunes
  - Other organ damage such as retina, heart, kidney?

→ SEE the disease
CEREBRAL AMYLOID ANGIOPATHY
“CAA is a common cause of lobar ICH”

30% of lobar ICH in the elderly?

562 ICH

196 lobar ICH (35%)
median age 75 (IQR 62-79)

29 (15%)
no CAA

120 (61%)
poss CAA

47 (24%)
prob CAA
How to diagnose CAA in patients with ICH?

Diagnostic criteria: the Boston criteria

Clinical diagnosis of cerebral amyloid angiopathy: Validation of the Boston Criteria

Article abstract—The authors performed clinical–pathologic correlation to assess the validity of the Boston diagnostic criteria for cerebral amyloid angiopathy (CAA). Thirteen subjects were diagnosed clinically with probable CAA from among 39 patients with available pathologic tissue in a prospective cohort of subjects aged ≥55 years with primary lobar hemorrhage. All 13 individuals were confirmed neuropathologically as having CAA. This small pathologic series indicates that the diagnosis of probable CAA can be made during life with high accuracy.

NEUROLOGY 2001;56:537–539
3. Probable CAA
   Clinical data and MRI or CT demonstrating:
   • Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed)
   • Age ≥55 years
   • Absence of other cause of hemorrhage‡

4. Possible CAA
   Clinical data and MRI or CT demonstrating:
   • Single lobar, cortical, or corticosubcortical hemorrhage
   • Age ≥55 years
   • Absence of other cause of hemorrhage‡
How to improve the Boston criteria? Superficial siderosis

Linn J. Neurology 2010
How to improve the Boston criteria? Superficial siderosis

Linn J. Neurology 2010
CAA : 2 FACES OF A DISEASE

- Occlusive expression of the disease

White-matter lesions
Small cortical infarcts
Microinfarcts (autopsy or high field MRI)

Gurol E. Ann Neurol 2012
CAA : 2 FACES OF A DISEASE

- Occlusive expression of the disease

White-matter lesions

Transient hypersignal DWI of presumed ischaemic origin

Microinfarcts (autopsy or high field MRI)

Smith E. Lancet Neurology 2012
CAA : 2 FACES OF A DISEASE

- Occlusive expression of the disease

White-matter lesions

Hypersignal in Double Inversion Recovery sequences

Yuichiro L. J Neuroimaging 2013
CAA : 2 FACES OF A DISEASE

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Cordonnier C. Brain 2010
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FORGET ‘PRIMARY’

Clues to the cause of ICH on CT

Aneurysm
Coagulopathy
Trauma
Venous thrombosis
Arteriovenous malformation
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<tr>
<th>Causes</th>
<th>No (% of patients (n=298))</th>
</tr>
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<tbody>
<tr>
<td><strong>Macrovascular:</strong></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>34 (11)</td>
</tr>
<tr>
<td>Dural arteriovenous malformation</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Cavernoma</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Cerebral venous sinus thrombosis</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Developmental venous anomaly*</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>69 (23)</td>
</tr>
<tr>
<td><strong>Other:</strong></td>
<td></td>
</tr>
<tr>
<td>Probable cerebral amyloid angiopathy27</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Hypertensive vasculopathy†</td>
<td>36 (12)</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Cocaine use</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Haemorrhagic infarction</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Unknown†</td>
<td>169 (57)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>229 (77)</td>
</tr>
</tbody>
</table>

*Partially thrombosed large developmental venous anomaly without evidence of adjacent cavernoma.
†Intracerebral haemorrhage in basal ganglia, thalamus, or posterior fossa in presence of hypertension.
‡In 30 of these patients, lobar haemorrhage in the presence of hypertension was observed.

Early CTA: diagnostic yield 17%
CTA/MR/DSA: 23%

Van Asch CJJ. BMJ 2015
HOW TO INVESTIGATE ICH PATIENTS?

- No consensus

  *Cordonnier C. Stroke 2010*

- CTA
  - identifies around ¾ macrovascular causes of ICH
  - widely available, feasible in patients with a poor clinical condition
  - few complications
  - BUT lower yield than expected

  *Van Asch CJJ. BMJ 2015*

- MRI/MRA
  - high accuracy for detection of macrovascular causes as a first diagnostic modality

  *Josephson CB. Cochrane Database Syst Rev 2014*
Markers of CAA?

- Lobar ICH
  - Yes
    - No indication of intracranial vessels investigation
  - No
    - Look at intracranial vessels

- MRI suggestive of a brain tumor or hemorrhagic transformation of an infarct?

- MRI (including MRV when cerebral venous thrombosis is suspected)
  - Deep ICH
    - White matter hyperintensities?
      - Yes
        - No indication of intracranial vessels investigation
      - No
        - Look at intracranial vessels
  - Lobar ICH
    - Signs of small vessel disease?
      - Yes
        - Repeat MRI and MRA in 3-6 months
      - No
        - Repeat DSA
  - If no feasible CTA
    - Normal
    - Repeat DSA

Example Lille Inhouse protocol

Domingues R. Neurol Clin 2015
Woman, 59 y

Hypertension treated with diuretics (blood pressure @ home: 130/90)

13h15: movements of the right superior lips (seizures?) during 30 min + dysarthria

Admission: 14h42,
- NIHSS 1 (dysarthria)
- BP: 160/100

Brain imaging: 14h58
TAKE HOME MESSAGE

- Forget Primary
- Ask the radiologist
  - Is there an underlying vascular lesion?
  - Is there a cerebral venous thrombosis?
- « What is the cause » will inform management & prognosis
  - Risk of recurrent ICH?
  - The cause will have impact on your management

FORGET ‘PRIMAR Y’
INTRACEREBRAL HAEMORRHAGE: WHAT IS THE CAUSE?

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