Brain imaging of microhaemorrhage in the Rotterdam Scan Study

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Cerebral microbleeds

- Hemosiderin: paramagnetic → disturbance of magnetic field
- T2*-weighted MR sequence: ‘black dot’
Microbleeds on MRI

T2

T1

T2*
Publications on cerebral microbleeds

# publications

1st detected on MRI

year

Microbleeds: clinical evidence

....associated with higher risk of (recurrent) ICH or ischemic stroke (Fan, Stroke 2003; Greenberg, Stroke 2004, Imaizumi, J Neurosurg 2004; Thijs, Stroke 2010)

....a risk factor for hemorrhagic transformation after ischemic stroke (Nighoghossian, Stroke 2002)

... conflicting evidence whether microbleeds may predict therapy-related bleeding complications (Kidwell, Stroke 2002; Fiehler, Stroke 2007; Lovelock, Stroke 2010; Bifi, Neurology 2010)

.. highly prevalent in persons with AD and related to cognitive function (Goos, Stroke 2009)
Many remaining issues...

• what is the prevalence (and incidence) of microbleeds in the general (stroke-free) population?
• what is the underlying etiology and what are risk factors for microbleeds?
• association with antithrombotic drugs?
• consequences/ clinical relevance: dementia? stroke?
the Rotterdam Study
the Rotterdam Study

55+ 1990-1993 7,983
   1994-1995
   1997-1999
   2002-2004
   2009-...

55+ 2000-2002 3,011

45+ 2006-2008 4,000
the Rotterdam Study

55+
1990-1993 7,983
1994-1995
1997-1999
2002-2004
2009-…

55+
2000-2002 3,011
2004-2005

45+
2006-2008 4,000

'95-'96 MRI
'99-'00 MRI
2005-… MRI (5,000)
the Rotterdam Scan Study

- goal: study causes and consequences of age-related brain changes
- cerebrovascular and neurodegenerative diseases
- investigating *imaging biomarkers* for brain disease
the Rotterdam Scan Study

- tissue quantification
- lesion detection
- microstructural quality
- incidental findings
- blood flow measurement
- microbleeds
### MRI detection of cerebral microbleeds

#### Conventional 2D T2* vs 3D High Res T2*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2D T2*GRE</th>
<th>3D T2*GRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR, ms</td>
<td>775</td>
<td>45</td>
</tr>
<tr>
<td>TE, ms</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>FA, degrees</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Matrix</td>
<td>256 * 256</td>
<td>320 * 224</td>
</tr>
<tr>
<td>Parallel imaging</td>
<td>No</td>
<td>Factor 2</td>
</tr>
<tr>
<td>Slice</td>
<td>5 mm</td>
<td>1.6 (0.8 mm)</td>
</tr>
<tr>
<td>Voxel size</td>
<td>0.5x0.5x5</td>
<td>0.5x0.5x0.8</td>
</tr>
<tr>
<td>Acquisition</td>
<td>2 min 29 s</td>
<td>5 min 55 s</td>
</tr>
</tbody>
</table>

**Images:**
- **Conventional 2D T2***
- **3D High Res T2***
MRI detection of cerebral microbleeds

<table>
<thead>
<tr>
<th></th>
<th>2D T2*GRE</th>
<th>3D T2*GRE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= 200</td>
<td>N = 200</td>
<td></td>
</tr>
<tr>
<td>≥ 1 microbleed, n (%)</td>
<td>42 (21.0)</td>
<td>71 (35.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>multiple, n (%)</td>
<td>19 (11.1)</td>
<td>43 (21.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>median number (IQR)</td>
<td>1.0 (1.0-4.0)</td>
<td>2.5 (1.0-9.5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Prevalence of microbleeds

Microbleed prevalence (%)

- Japan (1)
- Japan (2)
- ASPS
- Framingham
- AGES

Age (years)
Prevalence of microbleeds

Rotterdam Scan Study (n = 1,062)
1.6 mm (0.8 mm)

5 mm + 10% gap

Japan (2)
ASPS
Framingham

Japan (1)
AGES

Vernooij et al.; Neurology 2008
## Prevalence of microbleeds (n= 3,979)

<table>
<thead>
<tr>
<th>Age-range (yr)</th>
<th>No. of persons</th>
<th>Cerebral microbleeds</th>
<th>Multiple CMBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-50</td>
<td>413</td>
<td>6.5 (27)</td>
<td>0.7 (3)</td>
</tr>
<tr>
<td>50-59</td>
<td>1696</td>
<td>11.5 (195)</td>
<td>3.4 (57)</td>
</tr>
<tr>
<td>60-69</td>
<td>1350</td>
<td>16.8 (227)</td>
<td>4.9 (66)</td>
</tr>
<tr>
<td>70-79</td>
<td>377</td>
<td>28.9 (109)</td>
<td>14.9 (56)</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>143</td>
<td>35.7 (51)</td>
<td>22.4 (32)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3979</strong></td>
<td><strong>15.3 (609)</strong></td>
<td><strong>5.4 (214)</strong></td>
</tr>
</tbody>
</table>

Poels et al. Stroke 2010
Microbleeds: risk factors and etiology

- **lobar**
  - **APOE gene**

- **deep**
  - **hypertension, smoking, WML, lacunar infarcts**

- **infratentorial**
  - **Arteriosclerosis**

**Amyloid angiopathy**
Antithrombotic drugs and microbleeds

OR for presence of microbleeds

- **none**: $n = 699$
- **antiplatelet drugs**: $n = 245$
- **anticoagulant drugs**: $n = 61$
Antithrombotic drugs and microbleeds

- cross-sectional association
- no information on temporal relation
- confounding by indication?
- no information on subsequent risk of ICH
Posterior predilection of CAA pathology

PIB PET images

normal control  
CAA

Clustering of hemorrhages

Rosand et al. Ann Neurol 2005
Location of lobar microbleeds

Mesker et al. Arch Neur 2010
New microbleeds (3-yr interval)
New microbleeds (3-yr interval)

All participants (n=831)

- No incident microbleeds: 89.8%
- One incident microbleed: 4.6%
- Multiple incident microbleeds: 5.6%

Without microbleeds at baseline (n=628)
- No incident microbleeds: 94.6%
- One incident microbleed: 2.1%
- Multiple incident microbleeds: 3.3%

With microbleeds at baseline (n=203)
- No incident microbleeds: 74.9%
- One incident microbleed: 12.3%
- Multiple incident microbleeds: 12.8%
Microbleeds: prognosis

asymptomatic

CT scan 2 weeks later
Microbleeds: prognosis

- increased risk of stroke?
- relation with dementia?
- yes/no antithrombotic drugs
- aggressive treatment of cardiovascular risk
- preventive therapy
Work in progress

- automated microbleed detection
- association between microbleeds and cognition
- longitudinal imaging: incidence and progression of microbleeds
- ...microbleeds as risk factor for AD or stroke?
Conclusions

- detection of microbleeds depends heavily on MRI sequence
- prevalence of microbleeds in the general population is high
- etiology of microbleeds differs according to location
Conclusions

- Lobar microbleeds have a posterior predilection, similar to CAA pathology
- Microbleed development on MRI over a 3-year interval is substantial (about 10%)
- Association with antithrombotic drugs and prognosis of microbleeds needs to be further assessed in longitudinal studies
Collaborating researchers

Radiology
- Daniel Bos
- Piotr Wielopolski
- Marion Smits
- Aad van der Lugt
- Gabriel Krestin

Epidemiology
- Marielle Poels
- Ben Verhaaren
- Jory Hoogendam
- Bert Hofman
- Arfan Ikram
- Monique Breteler

Biomedical Imaging
- Marius de Groot
- Renske de Boer
- Fedde van der Lijn
- Stefan Klein
- Marleen de Bruijne
- Henri Vrooman
- Wiro Niessen
Imaging of Age-related Brain Changes
A Population-based Approach

Meike Vernooij

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The mission of population imaging is to help develop and implement strategies to prevent or effectively treat disease through creation of a world class imaging research infrastructure within or in close vicinity to large population studies in the Netherlands and Europe. By shifting the focus from curative to preventive medicine, it will in the short-term improve people’s quality of life and in the long-term reduce the costs for the healthcare sector.

www.populationimaging.eu