Cerebral small vessels

3D modeling of cerebral microvasculature

Variable density Cortex vs WM
Increase density with development
Definition of cerebral small vessels

- **Small arteries**: Ø 400 à 100 microns
  - External elastic coat (tunica elastica) + média (3-4 layers of smooth muscle cells)
- **Arterioles**: Ø < 100 microns
  - Thin or no external elastic coat, média with 1 or 2 layers of smooth muscle cells
- **Capillaries**: Ø < 10 microns
  - Lack of smooth muscle cells but surrounded by pericytes
Angioarchitecture
Angioarchitecture: key aspects for SVD

Long perforating arteries

Short perforating arteries
Distribution of lesions related to perforating arteries
Distribution of lesions in SVD

Amyloid angiopathy

Hypertension SVD
Cerebral small vessel disease

- **Acute**
  - Inflammatory / angiitis
    - Isolated angiitis of the central nervous system or systemic
    - Primary or secondary
      - Infections, autoimmune disorders, toxic origin, cancer …
  - Non-inflammatory
    - Susac’s syndrome (SICRET: Small infarction of cochlear retinal and encephalic tissue); Sneddon’s syndrome

- **Chronic**
  - Age and hypertension-related SVD (sporadic SVD)
  - Cerebral Amyloid Angiopathy (CAA)
  - Hereditary small vessel diseases (CADASIL and other CSVD)
Chronic cerebral small vessel disease
Age-Hypertension related SVD

Stroke

Ischemic Stroke

- 15% Primary Hemorrhage
  - Intraparenchymal
  - Subarachnoid

- 85%

- 20% Atherosclerotic Cerebrovascular Disease
  - Hypoperfusion
  - Arteriogenic Emboli

- 25% Penetrating Artery Disease ("Lacunes")

- 20% Cardiogenic Embolism
  - Atrial Fibrillation
  - Valve disease
  - Ventricular thrombi
  - Many others

- 30% Cryptogenic Stroke

- 5% Other, Unusual Causes
  - Prothrombic states
  - Dissections
  - Arteritis
  - Migraine/vasospasm
  - Drug abuse
  - Many more
Chronic cerebral small vessel disease
Age and hypertension related SVD

Wide spectrum of clinical manifestations and of MRI lesions

- **CLINICAL EVENTS**
  - Stroke (ischemic/hemorrhagic)
  - Depression
  - Gait disturbance
  - Balance problem
  - Cognitive decline

- **MRI**
  - Small deep infarcts
  - White-matter lesions
  - Micro and macrobleeds
  - Dilated perivascular spaces
  - Cerebral atrophy

Pantoni et al, Lancet Neurol, 2010
3 types of key cerebral lesions on MRI

- WM hyperintensities
- Microbleeds
- Lacunar infarction
Chronic cerebral small vessel disease
Age and hypertension related SVD (1)

T2 hyperintense WM lesions: increased risk of ischemic stroke

• The Rotterdam scan study
  • Population-based, 1077 pts 60-90 years
  • Follow-up: 4.2 yrs
    • 6% pts had more than 1 stroke during the follow-up: n = 57 events (42 ischemic, 6 hemorrhages, 9 undetermined)
    • No WML lesions: risk < 0.6% / year
    • Subcortial WML > 0.05 ml: risk x 1.4
    • Periventricular WML (confluent): risk x 2-3

* after adjustment for clinical and MRI variables

Vermeer et al, Stroke, 2003
Chronic cerebral small vessel disease
Age and hypertension related SVD (1)

T2 hyperintense WM lesions: increased risk of intracerebral hemorrhage

Atherosclerosis Risk in Communities (ARIC) Study and Cardiovascular Health Study (CHS) Population: 4872 participants (n = 1627 + 3245) with median 13 years FU

Folsom et al, Ann Neurol, 2012; 71: 552-559
Chronic cerebral small vessel disease
Age and hypertension related SVD (1)

T2 hyperintense WM lesions: increased risk of intracerebral hemorrhage

Atherosclerosis Risk in Communities (ARIC) Study and Cardiovascular Health Study (CHS) Population: 4872 participants (n = 1627 + 3245) with median 13 years FU

<table>
<thead>
<tr>
<th>WMH Grades</th>
<th>0–1</th>
<th>2</th>
<th>3</th>
<th>4–9</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>2,227</td>
<td>1,368</td>
<td>745</td>
<td>532</td>
</tr>
<tr>
<td>No subjects with IPH</td>
<td>17</td>
<td>18</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>IPH incidence rate per 10,000 person-years (95% CI)</td>
<td>7 (4–11)</td>
<td>11 (7–18)</td>
<td>23 (14–36)</td>
<td>27 (16–46)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1,00 reference</td>
<td>1,68 (0,86–3,30)</td>
<td>3,52 (1,80–6,89)</td>
<td>3,96 (1,90–8,27)</td>
</tr>
</tbody>
</table>

Adjusted for age, study, race, systolic blood pressure, current smoking, triglycerides, low-density lipoprotein cholesterol, fibrinogen, carotid intimal–medial thickness, and carotid plaque.

Folsom et al, Ann Neurol, 2012; 71: 552-559
Chronic cerebral small vessel disease
Age and hypertension related SVD (1)

T2 hyperintense WM lesions: association with cognitive decline

- CVH study, WML grade from 0 to 9, library of templates
  - Progression of WML: none: 1381, 1 grade: 458, ≥ 2 grades: 80
  - Significant after controlling for multiple variables including occurrence of infarcts

MMSE score

Digit symbol substitution test

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Longstreth, Stroke, 2005
Chronic cerebral small vessel disease

Age and hypertension related SVD (1)

Silent infarcts: prevalence

Increased risk of
- Ischemic Stroke
- ICH
- Cognitive decline
- Dementia

Figure 2: Prevalence of silent brain infarcts with increasing age, as reported in six population-based studies. HABS, Helsinki (Finland) Aging Brain Study; CHS, Cardiovascular Health Study; RSS, Rotterdam Scan Study; NILS-LSA, National Institute for Longevity Sciences-Longitudinal Study of Aging; MEMO, Memory and Morbidity in Augsburg Elderly study; and FHS, Framingham Heart Study.

Dilated perivascular spaces
Prevalence, risk factors and clinical significance in the 3C study

Prevalence of DPVS = 100%
Severity associated with age, male gender, hypertension
Severity associated with WMH and number of lacunar infarcts
High grade in WM associated with increased risk of incident dementia

Imaging and clinical predictors in sporadic SVD

- WM Hypertensions: 90-95%
- Silent Infarcts: 20-25%
- Ischemic stroke: 5%
- Vascular dementia: 1-2%
- Intra cerebral hemorrhage: Microbleeds
- Gait-balance pb
- Mood disturbances
- Mild cognitive impairment

Hypertension

Rotterdam - Cardiovascular Health - LADIS studies
Cerebral Amyloid Angiopathy

Prevalence from 65 to 85 years: 2.3% to 12.1% (no hemorrhage)

Aβ 39-43 fragment derived from APP (Aβ40 +++)

Arteries, veins or capillaries

CERAD - Ellis et al, 1996
Hereditary Cerebral Amyloid Angiopathy

Aβ

No CAA

Mild/Moderate CAA

Epsilon 4

Severe CAA vasculopathy

CAA related ICH

80-90% Alzheimer’s disease

20-40% Intracerebral Hemorrhage

Biffi and Greenberg, J Clin Neurol, 2011
Clinical manifestations related to CAA

- NONE
- Lobar hematoma (repeated)
- Cognitive decline (more or less severe / Alzheimer’s disease)
- Transient focal manifestations
Cerebral Amyloid Angiopathy

perivascular leakage of erythrocytes and plasma in presence of microbleeds

Greenberg, 2004
Sakurai et al, 2014
Research in SVD

Multiple questions and opportunities

- Identify the genetic factors involved in hereditary and sporadic SVD
- Determine the molecular mechanisms of vascular dysfunction in SVD
- Understand the mechanisms of cerebral tissue lesions and their dynamics with the progression of SVD
- Understand the mechanisms of clinical worsening and improve the clinical evaluation and prediction in SVD
- Develop new therapeutic approaches in preclinical models of SVD
- RCT for new preventive strategies in SVD patients
Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

Joutel et al, 1997; 2001, 2002
Missense **HTRA1 mutation** in CARASIL

High temperature requirement protein A1: serine protease involved in TGFβ signaling

A case report of a 34-year-old individual with alopecia before 18 years of age, unsteady gait, urinary urgency, and slurred speech.

**HTRA1 mutation**

- ↓ cleavage of **Latent TGFβ binding protein1**
- ↓ fibronectin binding to **LTBP-1** and ↓ incorporation of fibronectin in extracellular matrix

*Mendioroz et al, Neurology, 2010*

*Beaufort et al, PNAS, 2014*
Rare heterozygous variants of HTRA1 in familial SVD
Late age of onset

Verdura et al, Brain, 2015
Hereditary Cerebral Amyloid Angiopathy

No CAA → Mild/Moderate CAA → Severe CAA vasculopathy → CAA related ICH

Aβ

Mutant Cystatin C
Transthyretin
Gelsolin
Bri
Dan
PrP ...

Epsilon 4
**COL4A1 Mutation**

ICH through the skull in the mutant mice born naturally

No visible ICH with surgical delivery

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

Joutel et al, 1997; 2001, 2002
MODEL of pure VASCULAR DEMENTIA
- cognitive decline < 65 years
- pure vascular origin
- genetic marker for diagnosis

Chabriat et al, Lancet Neurol, 2009
LESION MAPPING DATA IN CADASIL

Extent of WMH is variable and may be associated with increased brain volume in CADASIL

Yao et al, Stroke, 2012
PROCESSING SPEED CLUSTERS PROJECTED ON THE ANTERIOR THALAMIC RADIATIONS AND FORCEPS MINOR IN CADASIL

Duering et al, Brain 2011
Cortex and cerebral atrophy are associated with clinical severity in CADASIL

Natural history of the disease

- Executive dysfunction
- Mid cognitive Impairment
- Moderate disability
- Severe disability
- Dementia
- WMH

Time:
- 10y
- 20y
- 30y
- 40y
- 50y
- 60y
- 70y
Natural history of the disease

- Executive dysfunction
- Moderate disability
- Severe disability
- Dementia
- Mid cognitive impairment
- Normal status

- WMH
- Lacunes
- Gait disturbances

- MEN
- WOMEN

- 10y, 20y, 30y, 40y, 50y, 60y, 70y
Natural history of the disease

Chabrier et al, Stroke, 2016
Treatments

• No specific treatment in sporadic SVD, CAA or in hereditary SVD

• Acute treatment in ischemic stroke
  – rtPA efficacy similar in small and large ischemic stroke
  – Hemorrhagic stroke: acute reduction of BP

• Preventive treatments
  – Efficacy previously detected in lacunar stroke as in other stroke subtypes (aspirin, clopidogrel, dipyridamole+aspirin)
  – Only a large RCT specific to ischemic SVD (small deep infarct)
Chronic cerebral small vessel disease
Age and hypertension related SVD (1)

T2 hyperintense WM lesions: progression altered by antihypertensive TRT

- 3C study: population-based cohort > 65 years, 1319 individuals, MRI FU 4 years
- use of antihypertensive TRT on the progression of WML

- systolic BP > 160 mm Hg, TRT started < 2 years
  - YES: + 0.24 cm$^3$ (0.44), NO: + 1.60 cm$^3$ (0.26); P = 0.0008

Godin et al, Circulation, 2011
SPS3 trial

No advantage of double antiplatelet treatment
No significant effect of blood pressure reduction after 3 years

Figure 1. Probability of the Primary Outcome.
The hazard ratio for the primary outcome, recurrent stroke, was 0.92 (95% CI, 0.72 to 1.2).
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