CADASIL, 30 years later

Shreveport, 2007

Marie Germaine Bousser
Hôpital Lariboisière, AP-HP, Paris

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
Our first patient: subcortical infarcts and leukoencephalopathy

- **1976**: 50 year old man, no vascular risk factor
  - lacunar infarct: (dysarthria - clumsy hand)
  - negative investigations (blood, CSF, heart, A°)
- >1977: migraine without aura
- **1983**: pure left sensory stroke
- >1984: progressive onset of: pseudo-bulbar palsy and sub-cortical dementia, total dependence, bedridden
- **1996**: death
The 2 children of our first patient

1987

N... 33 y.o. female >1983
- multiple episodes of transient dysphasia
- one pure motor minor stroke
- migraine with aura

No vascular risk factor
(except tobacco)

Negative investigations

1982: Dysarthria for 5 days

P.. 34 year old man

2006

N...- No other infarct
- depressed
- slightly deteriorated

P...Major stroke in 2002
  hemiplegic, demented, bedridden
First family: 57 subjects (clinical, MRI, genetics)

- 11 symptomatic (6 M, 5 F) age 43
- No or few vascular risk factors
- Clinical presentation:
  - subcortical ischemic events: 11
  - pseudo-bulbar palsy, subcortical dementia: 3
  - Migraine: 4, Epilepsy: 1
  - manic-depressive Sd: 1

MRI: white matter abnormalities: 19

Autosomal dominant transmission

Asymptomatic: 8
Symptomatic: 11
CADASIL (Family JN) Subject III 19

- 1971 : 40 year old female ans: Grand Mal seizure

- 1983 : Minor sub cortical infarct :
  right sensori-motor deficit and dysarthria

- 1985 : Epilepsy, manic-depressive episode

- 1986 : Multiple TIA : left sided numbness,
  Progressive subcortical dementia

- 1988 : 2 major strokes, tetraplegia,
  pseudo-bulbar palsy, dementia, bedridden

- 1990 : intracerebral hemorrhage, death (59y)
Subcortical white matter
- Leukoencephalopathy
- Thickening of the media of small arteries

Abnormal smooth muscle cells granular osmiophilic material (GOM)
1993 : CADASIL


Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) maps on chromosome 19q12

(Nature genetics 1993;3:256-259)
The story of CADASIL before CADASIL

• 1955 : Van Bogaert : “Binswanger in two sisters”
• 1977 : - Sourander “Hereditary multi-infarct dementia”
  - Stevens “Chronic familial vascular encephalopathy”
• 1980 : - Gerhard “Familiare zerebrale arteriosklerose”
  - Colmant « Familiare zerebrale gefässerkrankung »
• 1988 : Bousser et al: “Recurrent stroke in a family with diffuse WMA”
  stroke-like episodes and leukoencephalopathy”
• 1993 : Baudrimont et al: «Autosomal leukoencephalopathy and
  subcortical ischemic stroke»
Genetics of CADASIL

1993: 1 family: CADASIL gene located on chromosome 19 (Tournier-Lasserve... Bousser; Nature genetics)

1996: 33 families: gene identified: NOTCH 3 (Joutel et al)
CADASIL in 2007

- not such a rare disease, (familial and sporadic)
- expanded clinical spectrum
- diffuse arteriopathy (but purely cerebral signs)
- from subcortical ischemia to cortical changes
- smooth muscle cell disease
- impaired vascular mechanotransduction
- model of pure vascular dementia and for the evaluation of new tools in small artery diseases
- CADASIL type 2? (without Notch 3 mutations)
CADASIL: not such a rare disease

- Over 500 families worldwide, all continents, all races
- Large prospective cohorts: 156 in the French cohort (Chabriat)
- First randomised international trial: 168 patients in 18 months
- Sporadic cases of unknown frequency,

  - First sporadic case
  - 55 y old American man
  - 31-49 y: migraine with aura ± TIAS
  - 49 y: L sensori-motor facial deficit
  - 54 y: R dense hemiplegia
  - Skin biopsy: typical GOM
  - Typical MRI
  - Parents in good health

(Joutel et al Ann Neurol 2002)
## CADASIL: clinical signs

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n = 45 (23 M, 22 F)</td>
<td>n = 102 (42 M, 60 F)</td>
</tr>
<tr>
<td>Ischemic events</td>
<td>84 %</td>
<td>71 %</td>
</tr>
<tr>
<td>Subcortical dementia</td>
<td>31 %</td>
<td>28 %</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>22 %</td>
<td>33 %</td>
</tr>
<tr>
<td>Mood disorders</td>
<td>20 %</td>
<td>30 %</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>7 %</td>
<td>10 %</td>
</tr>
</tbody>
</table>

### Graphical Representation

- **Subcortical dementia**
- **Strokes**
- **Mood disorders**
- **Migraine with aura**
- **MRI lesions**

Years:

- Generation I: 50 ± 7 yrs
- Generation II: 48 ± 8 yrs

*P > 0.05*
Migraine and dementia in the same family

- **60 yo man** with migraine attacks since age 42
- Migraine with typical aura (1-5 / month)
  - Left visual field blurring of vision
  - Uni or bilateral tingling with occasional dysphasia.
  - Aura (<60 min) followed by headache + NVPP
- 2 atypical attacks with confusion and fever for 24 h
- NO HISTORY OF STROKE, DEPRESSION OR DEMENTIA

- **His sister 47-55y**
  - Progressive subcortical dementia
  - No migraine
  - No stroke
CADASIL, a diffuse arteriopathy (but purely cerebral signs)

Skin biopsy (Joutel, Lancet 2001)
Notch 3 monoclonal antibody immunostaining
Sensitivity: 96%
Specificity: 100%

Altered skin microcirculation reactivity (Gobron 2004)
Post occlusive hyperemia
Delayed response

Endothelium response to ACh: D peak-base
CADASIL, a diffuse arteriopathy 
(but purely cerebral signs)

Retinal abnormalities 
in 18 CADASIL patients 
(Cumurciuc et al JNNP 2004)

kidney
CADASIL: subcortical ischemic disease

Decreased CBF
Reduced increase (50%) after ACZ
MRI markers to distinguish CADASIL from arterio-sclerotic encephalopathy

Auer et al, Radiology, 2001
Sullivan et al, Neurology, 2001
MRI tensor diffusion in CADASIL

Increase in water mean diffusivity (MD) and loss of diffusion Anisotropy (1-VR) are more severe in demented patients

(Chabriat et al, Stroke: 1999)
Diffusion tensor imaging

Increase in diffusion over 3 years in a CADASIL patient

Molko et al
Stroke.2002
CADASIL: from subcortical ischemia to cortical changes

- **Brain volume loss**: mean annual rate: 0.56% (twice the controls) (Peters, Neurology 2006)

- **Cholinergic denervation** (post mortem case) (Mesulam et al, Neurology 2003)

- **Wide spread cortical neuronal apoptosis**: more extensive if larger load of subcortical ischemic lesions (Viswanathan et al, Stroke 2006)
CADASIL: a smooth muscle cell disease of small arteries

Transgenic mice carrying the Arg90Cys mutation

Ruchoux et al., Am J Path 2003
Natural history of vascular lesions in CADASIL

1- Smooth muscle cell changes

2- GOM

3- Notch 3 accumulation

4- Smooth muscle cell degeneration

Joutel et al, American Journal of Pathology, 2003
Early impaired vascular mechanotransduction in a transgenic mouse model of CADASIL

**Increase in myogenic tone**

**Decrease in flow -induced dilation**

**Permanent increased vascular tone?**

Dubroca et al, stroke 2005

Okeda et al, Stroke; 2002
CADASIL

**Notch 3 mutation**

- Impairement of structure and function of arterial smooth muscle cells
- Permanent increase in arterial tone
- Chronic subcortical ischemia
- Leukoencephalopathy
- Subcortical infarcts
- Neuronal apoptosis and cortical atrophy
TghN3R90C rescues arterial defects of N3-/- mice

- mN3+/+
- mN3+-
- mN3-/-
- mN3-/-;TghN3(WT)46
- mN3-/-;TghN3(WT)38
- mN3-/-;TghN3(WT)23
- mN3+/-;TghN3(R90C)
- mN3-/-;TghN3(R90C)ma
- mN3-/-;TghN3(R90C)ve
TghN3R90C rescues structural arterial defects of N3-/- mice
R90C mutation does not affect Notch3/RBP-Jκ activity
R90C mutant Notch3 remains functional despite Notch3\(^{ECD}\) accumulation and GOM deposits.

A novel pathogenic role for the mutant NOTCH3 protein?
CADASIL, a model of pure vascular dementia

- Silent infarcts: 20-25% *
- Lacunar stroke: 5% *
- White-matter changes: 90-95% *
- Va Dementia: 1-2% **

Similar MR changes on diffusion tensor imaging
Similar Cognitive impairment

> 60 years, general population, prevalence*
Rotterdam Study, CVH study
A novel hereditary small vessel disease of the brain unlinked to NOTCH3: (CADASIL type 2?) (Verreault et al Ann Neurol 2006)

- Case III-17
  - 50 y old man
  - no vascular risk factor
  - pure left-sided hemiparesis at 46 y
  - moderate impairment in executive dysfunction

- Case III-19
  - 54 yo woman sister of case III-17
  - No vascular risk factor
  - Sudden right hemiplegia with sensory deficit and dysarthria at 52

-Negative extensive work-up for usual causes of stroke
- Skin biopsy: no GOM (III-17)
- No Notch 3 mutation (III-17)
- 6 other affected members
CADASIL 30 years story: from patient to gene and vessel wall physiology

- First human disease due to Notch 3
- Autosomal dominant, sometimes sporadic, not so rare
- Diffuse disease of arteriolar smooth muscle cells
- Clinical expression purely in central nervous system
  
Subcortical infarcts, migraine with aura, dementia, mood disorders, starting in midadulthood, leading to death in 20 years
- Insight into migraine, mood disorders and Alzheimer’s disease
- Model of vascular dementia and for the evaluation of new tools
- Other autos. dom. families «CADASIL like» not linked to Notch3

From gene to pathophysiology and treatment?
Acknowledgements

- Hundreds of nurses, students, doctors and hospital staff over nearly 30 years in Salpêtrière, Saint Antoine and Lariboisière (Paris, France) ... and abroad
- Elisabeth Tournier-Lasserve, Hugues Chabriat, Anne Joutel, Katayoun Vahedi ... Martin Dichgans...
- Patients and families (particularly our first family)