

ULF Update talk on CADASIL: Biochemistry of CADASIL  
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Dr. Swati Sathe of the Department of Neurology, NYU School of Medicine gave a presentation near the end of the ULF conference held this summer, July 22, 2006. The talk is summarized here in the following sections.

1. CADASIL Symptoms and their age of onset
2. Brain MRI and CADASIL Progression
3. Molecular Defect: details of the Notch3 gene defect
4. CADASIL Pathology & Treatment

## 1 CADASIL Symptoms and their age of onset

In a study of 18 patients<sup>1</sup> divided into age ranges: <20, 20 – 29, 30 – 39, 40 – 49 and 50 – 59 years, the following symptoms were demonstrated most strongly within the decades as shown.

Symptom	Initial Symptoms Stratified by Age of Onset
<b>Migraine</b>	<20
<b>Stroke/TIA</b>	40 – 49
<b>Other (includes cognitive decline)</b>	40 – 49
<b>Depression</b>	50 – 59

Overall characteristics of a 76 member CADASIL group were as shown below.<sup>2</sup>

	Percent of Group
<b>CADASIL-related symptoms</b>	
TIA/stroke	76
Cognitive impairment	42
Migraine with aura	36
Major depression	11
Epileptic seizures	5
<b>Vascular Risk Factors</b>	
Smokers	36
Hypertension	24
Hypercholesterolemia	20
Diabetes mellitus	3

<sup>1</sup> Desmond: Stroke, Volume 30(6). June 1999. 1230 - 1233

<sup>2</sup> Peters N. et al., Stroke. 2004; 35:1603

## 2 Brain MRI and CADASIL Progression

Brain MRI images per Chabriat<sup>3</sup> demonstrate a pattern of increasing damage to the white matter at the center of the brain. This damage is consistent with the belief that capillaries collapse due to lack of support and there is loss of blood supply to the deep white matter, which is supplied by long penetrating blood vessels that do not form network. As a result their function cannot be taken over. The Brain MRI FLAIR image, per Gladstone JP et al.<sup>4</sup>, demonstrates hyper intensities in the anterior temporal poles characteristic of CADASIL.

The Van den Boom et al.<sup>5</sup> slide presents the correlation of specific MRI detectable damage by age. For 100% of all ages, areas of hyper intensity are visible. Micro bleeds are visible in about 20% of the 41 – 50 group. For ages 51 – 60, micro bleeds are visible in about 50% of the population studied. For ages 20 – 30, no lacunar infarcts<sup>6</sup> are seen, but for ages 31 – 60, lacunar infarcts are seen in 80% - 90% of the population studied. Sub-cortical lacunar lesions are visible with increasing age ranging from 20% for the age 20 – 30 group and increasing to 70% for the age 51 – 60 group.

## 3 Molecular Defect: details of the Notch3 gene defect<sup>7</sup>

The defective gene for CADASIL is located on chromosome 19p 13.1, the Notch3 gene. An alteration in the sequence (mutation) of this gene causes CADASIL; more than 75 such alterations have been described.<sup>8</sup> Notch3 encodes a glycosylated transmembrane receptor which is a protein involved in cell-fate specification during development. Specifically, the alteration in the sequence affects the body's ability to manufacture correctly the 2321 amino acid protein. Sixty-six percent of the mutations are in exon 4. Ninety-five percent of the mutations are missense mutations, that is, one amino acid in the sequence is replaced by another. Often this change involves a cysteine (which is an amino acid) residue i.e. either a cysteine is added or deleted.

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<sup>3</sup> Chabriat, H et al.: Neurology, 51(2). 1998: 452 - 457

<sup>4</sup> Gladstone JP & Dodick, DW. The Neurologist 2005; 11: 19 - 29

<sup>5</sup> Van den Boom et al., Radiology 2003; 229: 683-690

<sup>6</sup> Lacunar infarct – An area of tissue in an organ or part that undergoes necrosis following cessation of blood supply. This small infarct is usually located in the deep noncortical cerebrum or brain stem resulting from occlusion of the penetrating branches of the cerebral arteries.

<sup>7</sup> Joutel et al.; Nature 1996; 383:707-710

<sup>8</sup> Exon – An **exon** is any region of [DNA](#) within a gene, that is transcribed to the final [messenger RNA](#) (mRNA) molecule, rather than being [spliced](#) out from the [transcribed](#) RNA molecule. Exons of many eukaryotic genes interleave with segments of non-coding DNA ([introns](#)).

Eukaryotic - Cells containing a nucleus and other membrane-bound organelles

## 4 CADASIL Pathology and Treatment

The following slides from the presentation are presented verbatim.

### 4.1 Pathology

- Widespread angiopathy of small & middle-sized arteries
- Smooth muscle cells of the media replaced with deposits of basophilic granular material which is also electron-dense
- Reduplication of the internal elastic lamina
- Multiple small infarcts (lacunar, cystic), in the subcortical white matter, basal ganglia, thalamus
- Stains for amyloid negative
- Stains for myosin, collagen IV positive<sup>9</sup>

### 4.2 Sites of Extra neural Involvement

- Retina
- Heart
- Liver
- Skin
- Sural nerve
- Muscle

### 4.3 Early Diagnosis:

- Complicated migraine
- Family History of strokes at a young age
- Stroke at a young age in an individual with no risk factors

### 4.4 Treatment Possibilities

- Aspirin, Ticlopidine, Clopidogril to prevent stroke and coronary artery disease but there may not be an effective treatment for Micro bleeds
- Acetazolamide for cerebral vasodilatation (empiric therapy)
- Drugs to improve vascular reactivity
- HELP (Heparin-induced Extracorporeal LDL/fibrinogen Precipitation)
- Removal of the accumulated Notch3 extodomain
- Gene therapy with normal Notch3 gene
- Restore “Enhance of Split” function by gene therapy (a Notch3 signaling target)

### 4.5 Treatment for Agitation and Disruptive Behavior

- Risperidone (generic: Risperdal)
- Olanzapine (generic: Zyprexa)

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<sup>9</sup> Presentation delivered by Swati Sathe, M.D.

#### 4.6 Contraindicated in CADASIL

- Tricyclic antidepressants due to hypotensive effects<sup>10</sup>
- Fibrinolytic therapy due to the danger of bleeding
- Angiography due to complications in 69% of patients (vs. the general population risk of 0.5 – 5%) and permanent neurological deficit in 13%<sup>11, 12</sup>

#### 4.7 Medication Usage among 80 CADASIL Subjects<sup>13</sup>

	#	%
• Antiplatelet medication <sup>14</sup> (e.g. Plavix)	60	75
• Anticoagulants (e.g. Coumadin)	1	1
• Antihypertensives	17	21
• Statins	16	20

#### 4.8 Drug treatment for vascular dementia<sup>15</sup>

- |                  |                           |
|------------------|---------------------------|
| • Piracetam      | • Propentofylline         |
| • Oxiracetam     | • Aspirin                 |
| • Nicergoline    | • Triflusal               |
| • Citroline      | • <i>Ginko biloba</i>     |
| • Pentoxifylline | • Nimodipine              |
|                  | • Memantine <sup>16</sup> |

<sup>10</sup> Amytryptaline and Pamelor cause hypertension and dry mouth. Where once it was thought that the lower the blood pressure, the better; the current thinking is that blood pressure should be around 120/80; not too high and not too low.

<sup>11</sup> Dichgans & Peteresen, Lancet 1997; 49: 776-777

<sup>12</sup> In CADASIL strokes are small so there's nothing to open up via angiography

<sup>13</sup> Peters, et al., Stroke, 2004; 35: 1603-1608

<sup>14</sup> Dr Swati Sathe recommends that all CADASIL patients take an antiplatelet medication.

<sup>15</sup> Adapted from: Roman et al., The Lancet Neurology 2002; 1: 426-436

<sup>16</sup> Memantine is used with Aricept for moderate to severe dementia

#### **4.9 Diagnostic Approach to CADASIL**

- Genetic Testing
  - Screening of the 4 exons most commonly affected has false-negative rate of 20%
  - Screening 23 exons has a sensitivity of 95% and specificity of 100%
- Skin or muscle biopsy
  - Granular osmiophilic material seen on electron microscopy (sensitivity 50%; specificity 100%)
  - Tissue samples can be stained with monoclonal antibodies to Notch3 protein in certain centers (sensitivity 96%; specificity 100%)