

CADASIL TOGETHER WE HAVE HOPE NONPROFIT ORGANIZATION
NEWS INFORMATION
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Interesting article published in 2008, **highlights the birth of CADASIL**

Marie-Germaine Bousser: going against the grain

In May this year, near the city of Nantes in western France, a rare family union of more than 120 members was taking place. As a friend of the family, Marie-Germaine Bousser, head of the Neurology Department of the Hospital Lariboisière in Paris, was one of the few invited guests. "It was a special occasion, and I felt extremely honoured to be invited", says Bousser. Her friendship with the family dates back to 1976 when one of the family members, Mr C, walked into the neurologist's clinic. At that time, neither realised that this encounter would drastically change both of their lives and would have important implications for the medical field.

"He had a strange condition", recalls Bousser. Soon after having had a stroke, Mr C showed signs of Binswanger's disease—a small-artery disease associated with hypertension and dementia—but his blood pressure was normal. Bousser enrolled Mr C in a clinical trial that she and her colleagues were running to investigate the efficacy of aspirin in preventing recurrent stroke, and followed him closely. His condition progressively deteriorated and his puzzling symptoms continued to trouble Bousser for years.

The turning point came 9 years later when Mr C's children came to Bousser with similar symptoms. "I realised then that this might be an unknown condition that ran in the family", she says. In collaboration with Elisabeth Tournier-Lasserre, a Paris-based geneticist at INSERM (French National Institute for Health and Medical Research), Bousser studied 57 adults of the family. In 1993, they mapped the mutated gene on to chromosome 19, and 3 years later, with their co-worker Anne Joutel, also at INSERM, they identified the gene as Notch3—a gene that had previously been thought to be expressed only in fruit flies.

Bousser and Tournier-Lasserre named the condition CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), which has subsequently been identified in hundreds of families worldwide. The clinical features of CADASIL are now well characterised, and include subcortical stroke, migraine with aura, psychiatric disturbances, and, at the late stage of development, dementia.

The discovery of the role of Notch3 in the smooth muscles of small blood vessels in human beings was a eureka moment in Bousser's clinical career, and the finding has furthered the understanding of some basic biological questions. "In effect, this was translational research in reverse: from bedside to bench", she remarks. Bousser is now working with Tournier-Lasserre and Joutel on mouse models of CADASIL, in which Notch3 is either mutated or deleted. "I hope we will be able to find a cure to treat this severe condition", says Bousser.

CADASIL is related to another of Bousser's long-term interests, migraine, particularly the link between stroke and migraine with aura. Her research group has shown in two case-control studies that there is a statistically significant association between CADASIL and migraine in young women. Interestingly, a third of the patients in Mr C's family also has migraine with aura, whereas the frequency rate in the general population is less than 10%. "This is interesting", says Bousser. "But we don't yet know why one third of CADASIL patients have migraine with aura."

Ongoing studies of CADASIL in animals might give some clues to the mechanism of migraine in this condition.

Bousser was also among the first neurologists to raise awareness of stroke in women. In the early 1980s, aspirin was thought to be effective in decreasing stroke recurrence only in men. Bousser's study, however, showed that a similar efficacy of aspirin in decreasing stroke recurrence was also observed in women. In 1997, to an audience of thousands of clinicians at the Scientific Sessions of the American Heart Association, she delivered the prestigious Paul Dudley White International Lecture on stroke in women.

"I was struck by the fact that little attention had been paid to this problem in women", says Bousser. By that time, the two main clinical trials on aspirin in primary stroke prevention—the US and British studies, published in the late 1980s—recruited only male participants. By contrast, the first study on aspirin in the primary prevention of stroke in women was not published until 2005.

"More women than men are likely to die from stroke because they live 10 years longer", she adds. Fortunately, campaigns such as Bousser's have made a difference: it is now a topical concern, with numerous researchers around the world working on stroke prevention and treatment in women.

To recognise her outstanding achievements in stroke research, Bousser was awarded the 2008 Johann Jakob Wepfer Prize, which was created by the European Stroke Conference in memory of the Swiss pathologist who first hypothesised that stroke was caused by bleeding in the brain. In addition to her clinical and academic excellence, it is perhaps also Bousser's compassion for patients and her courage to go against the grain—with her persistence in working on neglected diseases and in campaigning for the health care of women—that have continued to propel her to new heights.

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