CADASIL

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In this issue of the Swiss Medical Weekly Michail Vikelis and coworkers publish a novel mutation causing CADASIL [1]. Why publish a case report on a disease that is well known in the neurological community, when there are already more than 70 known mutations, associated with the phenotype of CADASIL? There are two reasons. First, for geneticians performing genetic tests it is important to know the existence of this mutation and where to search for mutations. Second, the editorial board felt that CADASIL should be brought to the attention of the community of internal medicine.

Decades ago various researchers reported on the occurrence of strokes, arteriosclerotic leukoencephalopathy or multi-infarct dementia among multiple family members in a pattern consistent with autosomal dominant inheritance. The acronym CASADIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) was created (Marie-Germaine Bousser, personal communication), and Tournier-Lasserve et al. mapped the disease locus to chromosome 19q12 in two unrelated families [2]. Chabriat and coworkers [3] used MRI and genetic linkage analysis to study 45 patients of 7 CADASIL families with 148 members and found strong linkage to chromosome 19. One year later, the same research group from the Lariboisière Hospital in Paris characterised the human Notch3 gene and Notch3 gene mutations in CADASIL patients as the cause of the disorder [4]. Since then, CADASIL is the model disease of a monogenic hereditary stroke disorder.

What is the function of the Notch3 gene? The Notch3 gene provides instructions for making a receptor protein, the Notch3 receptor, which is located at the surface of smooth muscle cells surrounding arteries. Notch3 receptors play a key role in the development, survival and function of vascular smooth muscle cells of arteries, especially in the brain. Dysfunction of Notch3 receptors leads to the phenotype of CADASIL.

The pathological findings of CADASIL include granular, eosinophilic deposits in the tunica media of smaller arteries in the brain, skeletal muscle, and skin. The illness often begins with complicated migraine attacks in young adulthood, later followed by clinically overt strokes. Progressive pyramidal and extrapyramidal motor signs and sensory and cognitive deficits ensue, typically leading to death by age 60 or 70. Men tend to die earlier than women [5]. MRI reveals signal changes like those of microangiopathy of other causes; a distinct feature of CADASIL is that small vessel disease is additionally seen in the temporal poles and external capsules[1].

There is no cure for CADASIL. Symptomatic treatment and prevention include general measures and drugs as in any other patient with migraine, stroke or dementia. Furthermore, a profound knowledge of the disease and its natural history is important for caring and counselling CADASIL patients and their families.

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