The First Indian-Origin Family with Genetically Proven Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

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We report the first family of Indian origin known to be affected by cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Seventeen members of the family spanning 3 generations had neurologic syndromes compatible with CADASIL, of whom 5 were genetically confirmed carriers of the *Notch3* gene R141C mutation in exon 4 ($421^{C \rightarrow T}$ and $141^{Cys \rightarrow Arg}$). Our report highlights that CADASIL not only occurs sporadically in South Asians, but also may account for stroke in South Asians with a strong family history. Furthermore, the similarity of clinical presentations described here to those typical for Caucasian case series suggests that the CADASIL phenotype is preserved across racial groups. **Key Words:** *Notch3*—stroke—gene polymorphism—South Asian—small vessel disease—familial inheritance.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common Mendelian form of hereditary small-vessel disease and vascular dementia and is caused by one of more than 100 mutations in the *Notch3* gene lying on chromosome 19q13.1.[1-3] *Notch3* mutations lead to accumulation of the Notch3 protein ectodomain at the cytoplasmic membrane of vascular smooth-muscle cells in cerebral vessels, resulting in arteriopathy.[4] These protein accumulations can be visualized by electron microscopy, characteristically as granular osmiophilic deposits.[5]

Although the vast majority of CADASIL studies to date have described patients of European origin, cases have been reported from all continents worldwide. The number of reported cases from locations outside Europe has recently increased as the condition becomes more widely recognized. Three case reports of CADASIL in individuals of South Asian ancestry have been published,[6-8] of which 2 were genetically confirmed. However, in these cases, CADASIL was not genetically diagnosed in other family members, suggesting possible sporadic occurrences.

Here we report a genetically proven CADASIL family of Indian origin carrying the R141C mutation in exon 4 of the *Notch3* gene. To the best of our knowledge, this is the first genetically characterized complete CADASIL family of South Asian descent. The study is important in revealing the form of CADASIL presentation in South Asians with a diagnosis based on other factors than simply similar features to the stereotypical European pattern of CADASIL.

Case Description

History

The proband is a 58-year-old Indian male born in Uganda, Africa to Gujarati Indian parents who

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immigrated to England in 1972. He presented in 2000 with a 12-month history of migraine-like headaches and memory impairment. He had a 30-year history of epileptic seizures and a previous history of hypertension. In 2003, he was treated for vitamin B12 deficiency and probable stroke. In 2008, he complained of a progressive deterioration in walking associated with left leg spasticity of several years' duration. Two years later, he returned with a new complaint of typical migraines without aura.

Family History

The proband had a strong family history of stroke-like symptoms with at least 17 affected family members (Fig 1). The family were practicing Hindus and followed a predominantly vegetarian diet. The proband's parents (designated I-B and I-C) were unrelated and died of a heart attack and stroke, respectively. All brothers were thalassemic, and 2 (II-0 and II-P) were genetically diagnosed with CADASIL with onset after age 45 years. One brother (II-S) and 1 sister (II-L) also sustained stroke and were suspected of having CADASIL; however, they could not be tested for *Notch3* mutations. Several distant maternal family relatives also had consulted a neurologist in the past. All maternal sisters (I-D, I-E, I-F, and I-G) died of stroke. Three maternal cousins (II-D, II-E, and II-F) were diagnosed with CADASIL, and 4 other cousins (II-G, II-I, II-J, and II-K) suffered from neurologic disorders and paralysis. All 3 cousins with CADASIL suffered from migraine, transient dementia, memory loss, and depression. The youngest cousin (II-F) experienced severe weakness of both lower limbs and was unable to walk down sloping surfaces. He also suffered from urinary and fecal incontinence.

Examination

Physical examination of the proband revealed a blood pressure of 112/79 mm Hg and regular pulse with a rate of 89 beats/minute. Bilateral gaze evoked nystagmus in the horizontal plane was present. Tone was increased in the left leg, but power was preserved throughout. Reflexes were brisk but equal bilaterally. Finger jerks were noted bilaterally. Both plantar responses were flexor. There were no cerebellar signs, but the patient had some difficulty performing heel-to-toe walking. There were no other consistent cerebellar signs. Rhomberg's test was negative.

Results

The proband demonstrated a confirmed thalassemia trait with microcytic anemia. His total cholesterol was 4.7 mM/L. The following blood tests were normal or negative: Factor V Leiden mutation, Prothrombin mutation, Protein S free antigen, Protein C activity, antithrombin activator, lupus inhibitor, autoantibody screen (including anti-dsDNA, ANA, and cytoplasmic antibodies), kaolin clotting time, protein electrophoresis, homocysteine (12.20 μmol/L) angiotensin converting enzyme, thyroid function tests, urea and electrolytes, liver function tests, immunoglobulins, erythrocyte sedimentation rate (5 mm/hour), and serum glucose (6.4 mM/L).

Detailed neuroimaging revealed extensive white matter changes with a lacunar state involving the posterior fossa as well as the deep brain structure. Spinal magnetic resonance imaging showed some lower cervical degenerative changes and mild compression at C5/6 and C6/7 but with no any intramedullary signal changes. Carotid

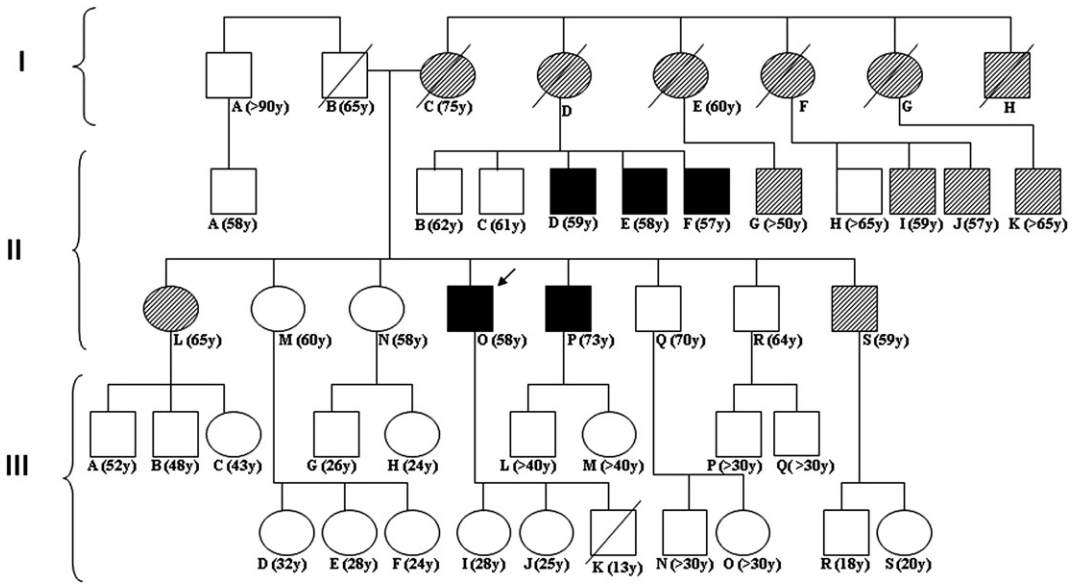

Figure 1. *Pedigree chart showing 3 generations of family members of the proband (arrow) affected by neurologic problems (shaded) and genetically confirmed CADASIL (black). Unaffected family members are in white. Age in years is presented alongside each individual. Family members I-C–I-H died due to stroke, and member I-H suffered from unexplained neurologic problems at a young age. Members II-G, II-I, II-J, II-L, and II-S suffered from stroke, and member II-K suffered from paralysis, however none were genetically tested for CADASIL. Member III-K died in a car accident.*