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The first report of CADASIL in Peru: Olfactory dysfunction on initial presentation

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ABSTRACT

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a rare, heritable, small vessel vascular disease caused by mutations in the *Notch3* gene that is characterized by migraines, subcortical vascular events, cognitive decline, and mood disturbances. However, many CADASIL cases present with unusual symptoms such as status epilepticus, a movement disorder, or sensory dysfunction. This study describes the clinical, genetic, and radiologic characteristics of a Peruvian family with CADASIL in which multiple family members presented with severe olfactory deficits. Seven members of the family have symptoms suggestive of CADASIL, with genetic testing revealing R133C mutations in the two patients who underwent genetic testing. Cognitive testing and olfactory identification testing (Smell Identification Test) were performed in three CADASIL patients revealing total anosmia in two tested patients and severe hyposmia in the other. Olfactory dysfunction has been associated with various neurologic and psychiatric conditions, though few studies have linked it with neurovascular disorders such as CADASIL. This first reported case of CADASIL in Peru emphasizes that symptomatic olfactory dysfunction may be an unusual presentation of CADASIL and that olfactory dysfunction is important to evaluate in CADASIL patients.

1. Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL)[1] is the most common heritable cause of neurovascular disease. CADASIL is caused by a mutation in the Notch homolog 3 gene (*Notch3*) on chromosome 19p13.1, which codes for a transmembrane receptor predominantly expressed in systemic arterial smooth muscle cells [1]. Though CADASIL has been described in over 500 families worldwide, the overall prevalence of the disease is unknown. Studies in Scotland [2] and England [3] have provided an estimated prevalence of 1.32–4 cases per 100,000 adults in these populations, but there are fewer reported cases outside of Western Europe, and no prevalence estimates for South American populations.

The clinical course of CADASIL is highly variable, though it is typically characterized by five primary symptoms: migraine with aura, subcortical ischemic infarcts, apathy, mood disturbances, and cognitive decline [4]. Subcortical infarcts including lacunar cerebral infarcts and transient ischemic attacks (TIAs) are the most common symptoms in CADASIL, occurring in 60–85% of patients. Stroke and TIAs typically strike those over the age of 40 or 50, while migraine tends to be an early symptom, sometimes even occurring before the age of 20 [4]. Other commonly described symptoms include vascular dementia and mood disturbances such as depression, bipolar disorder [5], and apathy [4]. Some case reports have also described unusual presentations of CADASIL such as facial dystonia [6], status epilepticus [7], status migranosus [8], sensorineural hearing loss [9], reversible coma and confusion [10,11], and olfactory dysfunction [12].

Olfactory dysfunction in particular is associated with normal aging as well as migraines [13,14], cognitive impairment [15,16], various neurodegenerative diseases [17–20], and to a lesser degree, stroke [16,21,22]. Although multiple case reports and smaller studies have reported

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[1] Abbreviations: a) Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), b) Mini Mental Status Examination (MMSE), c) Montreal Cognitive Assessment (MOCA), d) Instituto Nacional de Ciencias Neurologicas (INCN), d) University of Pennsylvania Smell Identification Test (UPSIT).

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olfactory deficits associated with strokes, population-based studies have been more ambiguous regarding this association: Wehling et al. [22], Murphy et al. [21] and Karpa et al. [16] found stroke to be significantly associated with olfactory dysfunction, while Landis et al. [23] and Schubert et al. [24] did not. Case reports describe olfactory dysfunction occurring with strokes located in the bilateral thalami [25,26], the left insula [27], and the insular frontoparietal region [28], among other regions. Many of these case reports describe altered or unpleasant olfactory perception rather than loss of olfactory identification abilities [22, 26–28]. Increased olfactory dysfunction on smell identification testing in patients with CADASIL compared to control patients has been found in a single previous study [12], however there have been no reports of patients with CADASIL presenting with spontaneous complaints of abnormal smell sensation.

Smell disorders include anosmia (total olfactory dysfunction), hyposmia (incomplete olfactory dysfunction), and dysosmia (distorted olfactory sensation). Dysosmias can be parosmias (with an odor stimulus) or phantosmia (without odor stimulus). Testing of olfactory function can be conducted using olfactory identification testing or olfactory threshold level testing. However, olfactory identification is a more clinically sensitive indicator of central olfactory function and has been shown to directly correlate with olfactory threshold testing [29]. In this report, we present the first family with CADASIL in Peru, in which two members presented spontaneously complaining of severe olfactory deficits.

2. Methods

This study was approved by the Ethics Committee of the Instituto Nacional de Ciencias Neurologicas in Lima, Peru. The study evaluated a single family (Fig. 1) that has been followed at the Neurogenetics Research Center of the Instituto Nacional de Ciencias Neurológicas since 2013 [30]. Two patients underwent mutational screening for *NOTCH3* at the Laboratoire de Genetique Moleculaire of the Hôpital Lariboisiere in Paris, France using previously described methodology (http://hopital-lariboisiere.aphp.fr/biologie-imagerie/genetique-moleculaire-neurovasculaire-lariboisiere). Other family members with consistent symptomatology and neuroimaging were given a presumptive clinical diagnosis of CADASIL. All patients underwent complete neurologic examinations. Additional clinical data was gathered from retrospective chart review. MRI imaging data was obtained from the clinical chart when available.

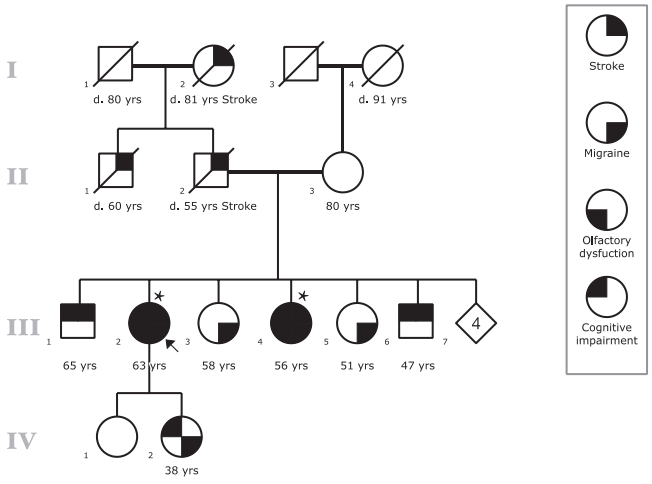

Fig. 1. Pedigree of the CADASIL affected family.

After obtaining written informed consent, three symptomatic patients also participated in prospective cognitive testing and olfactory identification testing. Olfactory identification was assessed using the previously validated and Spanish-translated 40-item forced choice test: the Smell Identification Test, previously known as the University of Pennsylvania Smell Identification Test. This test involves the presentation of 40 common odorants in a scratch and sniff booklet, with patients given a score based on how many they can identify correctly. Raw scores are scaled by gender and age based on preexisting data gathered from international control subjects [29]. Medical history relevant to olfaction, including history of nasal polyps, sinusitis, rhinitis, smoking, drug use, alcohol abuse, head trauma, and nasal surgery was also elicited. Spanish language versions of the Mini Mental Status Examination (MMSE) and the Montreal Cognitive Assessment (MOCA) were used to evaluate global cognition [31,32].

3. Results

The proband (III2), five other siblings in one generation of the CADASIL-affected family, and one additional patient in the next generation were found to have CADASIL-consistent symptoms. 4 of 7 (57%) of affected patients had at least one stroke, 5 of 7 suffered migraines, 2 of 7 complained of symptomatic olfactory dysfunction, and 5 of 7 experienced memory loss or cognitive impairment (Table 1). The family reports mestizo, or “mixed race” ancestry. Genetic sequencing of patients III2 and III4 revealed the known CADASIL mutation of c.475C>T in exon 4 of the *NOTCH3* gene leading to the replacement of an arginine (CGC) by a cysteine (TGC) at position 133 (P.R133C) of the NOTCH3 protein. Olfactory identification scores, scaled percentile rank, and MMSE and MOCA scores are shown in Table 2.

4. Case presentations

4.1. Proband (III2)

The proband is a 63-year-old woman with a history of stroke in her mother and maternal grandmother, but no history of hypertension, drug use, smoking, or alcohol use. At age 59, she awoke one morning with numbness and weakness on her left side and was hospitalized for a stroke. She reported a total loss of smell and taste sensation, particularly for salted foods, beginning at that time. She denies any history of head trauma, rhinitis, sinusitis, or nasal polyps. She also notes that she has had progressively worsening memory problems and difficulty with spatial orientation since that first event. An initial neurologic examination revealed left-sided hemiparesis, hemihypoesthesia, and hyperreflexia as well as a left-sided Babinski sign. Additional complaints included decreased visual acuity, frequent numbing episodes in her right hand, depressive episodes, and disordered sleep. An MRI showed a subacute ischemic stroke in the left subcortical parietal region, as well as ischemic foci of greater chronicity (Fig. 2). A complete symptom profile (Table 1) and results of cognitive testing and olfactory identification testing (Table 2) are shown above.

4.2. Subject III1

Subject III1 is a 65-year-old man with a history of hypertension who had an acute intracerebral hemorrhage at the age of 60 resulting in left-sided hemiparesis and moderate dysarthria. He currently has significant cognitive decline as well. He denies symptomatic olfactory changes, however he was found to have olfactory dysfunction on olfactory identification testing (Table 2). He denies any history of migraines, but has had some mood disturbances in the past. A neurologic examination reveals hemiparetic gait and left-sided hyperreflexia and weakness. MRI imaging shows extensive areas of gliosis in both cerebral hemispheres associated with lacunar infarcts in the right thalamus and right caudate nucleus, as well as a lacunar infarct in the left caudate nucleus. The

Table 1
Clinical and molecular characteristics of 5 CADASIL patients.

Patient ID	Sex	DNA test	Age of onset	Feature at onset	Age at exam	Dx. duration (years)	Migraine	Stroke	Cognitive decline	Mood changes
III1	M	N	60	Stroke	65	5	−	+	+	+
III2	F	Y	59	Stroke	63	4	−	+	+	+
III4	F	Y	18	Migraine w/o aura	56	38	+	+	+	+
III6	M	N	44	Stroke	48	4	−	+	+	−
IV2	F	N	10	Migraine	37	27	+	+	+	−

lateral ventricles are asymmetrically enlarged. Although definitive diagnosis with genetic testing was not obtained for this subject, III1 scored 17 out of 25 points on the CADASIL scale, highly suggesting that he has CADASIL [33].

4.3. Subject III4

Subject III4 is a 56-year-old woman with a history of dyslipidemia and prior tobacco use who has had severe weekly headaches associated with nausea, photophobia, and sonophobia since her teenage years. 3 years ago, she began having pain, numbness, and tingling in both her inferior and superior extremities. In the past year, she has also had memory loss and began complaining of the disturbing sensation of "smelling death" when smelling strong odors. She also notes that she has diminished taste for food, blurry vision, and dressing apraxia. MRI imaging shows generalized bilateral leucoencephalopathy, particularly in the temporal and frontoparietal areas and in the corpus callosum (Fig. 2).

5. Discussion

Although CADASIL has been described in families worldwide, few South American cases have been reported. To our knowledge, the first case of CADASIL on the continent was described in Uruguay in 1999 [34], while subsequent cases have been reported in Argentina [35,36], Colombia [37], Brazil [38], and Chile [39]. However, no cases have previously been described in Peru.

The Peruvian CADASIL-affected family described in this case harbors a C457T in exon 4 of *NOTCH3* gene, leading to the substitution of an arginine (CGC) by a cysteine (TGC) at position 133 (P.R133C) of the NOTCH3 protein. This mutation, as well as over 150 other pathogenic mutations, is localized between exons 2 and 24 in the predicted ligand-binding domain of the epidermal growth factor-like repeats of NOTCH3 protein. The mutation causes a change in a number of cysteines, leading to damage in the CADASIL-affected small arteries [40–42].

The R133C mutation has never been described in South America. However, it is common on a global level as the predominant gene in Finnish families [43], and is also present in Korean [44], Japanese [45], and Chinese [46] CADASIL-affected families. Among the South American cases that report the precise CADASIL-causing mutation, there is little overlap, with described mutations including R1031C [47], R141C [6], C455R [37], R153C [38], C251S [34], and with this case, R133C. The variety of CADASIL-causing mutations in South America makes it less likely that these CADASIL cases are interconnected, and instead suggests the presence of multiple unrelated de novo mutations or founder's effects on the continent. Genomic analysis of the Peruvian population, the majority of which identify as "mestizo," or "mixed race," reveals that around 83% of the mestizo genome traces back to Amerindian background, while 1–5% is East Asian, and the remainder is European [48]. There were large waves of Japanese and Chinese migration to Peru in the 1900s, and given the presence of the R133C CADASIL mutation in various East Asian populations, this Peruvian case may be traceable to this East Asian migration. The mutation could also represent a de novo mutation in the Amerindian population, or a founder's effect dating to the time of European colonization.

The severe olfactory dysfunction associated with CADASIL in three patients in this Peruvian family is notable. Two patients came in with a spontaneous complaint of olfactory and gustatory dysfunction. Patient complaints of symptomatic olfactory dysfunction have not been previously reported with CADASIL. One patient (III2) complained of total anosmia with decreased gustatory sensation, while the other (III4) complained of decreased, but not absent olfactory and gustatory sensation as well as a specific kind of dysosmia — sensing the "smell of death". A third patient was unaware of his total anosmia, which was revealed with smell identification testing, though this may be partly explained by his cognitive compromise. Both cognitive dysfunction and stroke are associated with olfactory dysfunction. However, these are usually subtle olfactory identification deficits, and not prominent symptoms for the patients. The combination of dysosmia and dysguesia further supports the idea that these patients have true olfactory and gustatory dysfunction rather than simple cognitive compromise.

Severe hyposmia or anosmia alone can be expressed as loss of taste sensation, which is what likely occurred in these cases given the temporal correlation of the two symptoms [49]. The coexistence of olfactory and gustatory deficits here is unsurprising because taste is a product of multisensory cortical integration of taste bud chemoreceptors, as well as olfactory and somatosensory afferents to the cortex [50]. The olfactory system processes information about the identity, concentration and quality of chemical stimuli, or odorants. Odorants are recognized by neuronal receptors in the olfactory epithelium of the olfactory bulb, which projects to the piriform cortex in the anterior medial temporal lobe, as well as to the orbitofrontal cortex and subcortical structures of the amygdala and hypothalamus [51]. MRI studies in CADASIL patients tend to show frontal, parietal and anterior temporal white matter lesions, and many of these lesions show significant overlap with areas implicated in olfaction [52]. A Korean study on CADASIL compared olfactory dysfunction with MRI imaging and found that olfactory dysfunction in CADASIL patients correlated with increased frontal and anterior temporal white matter lesion severity, which is also consistent with the neuroimaging and olfactory testing in this study (Fig. 2). The Korean study further showed overall lower scores in CADASIL patients compared to control patients on their olfactory identification test, though the difference was mild. The study did not comment on subjective patient complaints of dysosmias or loss of smell sensation. Other than this study, conducted in a single medical center in South Korea [12], olfactory symptoms have not been previously described in case reports

Table 2
Cognitive, olfactory, and gustatory characteristics of CADASIL patients.

Patient ID	Sex	Age at eval.	MMSE	MOCA	Reported smell deficit	Reported taste deficit	UPSIT raw score	UPSIT %	Olfaction result
III1	M	65	22	17	None	None	15	5%	Total anosmia
III2	F	63	27	24	"I cannot smell"	"Can't taste salted foods"	13	5%	Total anosmia
III4	F	56	24	21	"Everything smells like death, ugly"	"Can't taste food well"	24	8%	Severe microsmia

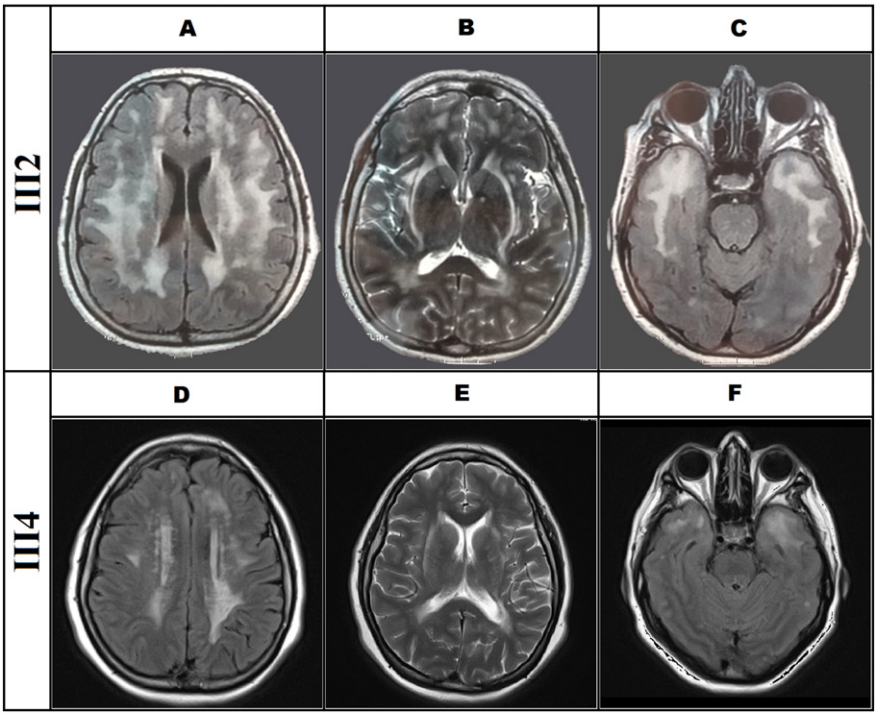

Fig. 2. MRI imaging of two affected family members. Subject III2: (A) Axial fluid-attenuated inversion recovery (FLAIR) sequence with severe leukoencephalopathy and multiple subcortical infarcts; (B) axial T2-weighted sequence with bilateral lesions in the external capsules; (C) axial FLAIR sequence with bilateral lesions of the temporal lobes at the anterior pole. Subject III4: (D) Axial FLAIR sequence with moderate leukoencephalopathy and some subcortical infarcts; (E) axial T2-weighted sequence with bilateral involvement of external capsules; (F) axial FLAIR sequence with bilateral involvement of the anterior pole of the temporal lobes.

from any other patient populations or in any of the large previous studies of clinical symptomatology in CADASIL [53]. The presentation of this Peruvian family with symptomatic olfactory dysfunction supports the idea that this deficit may be more widespread and significant than previously appreciated. It is likely that these olfactory deficits may occur due to stroke-like events in the orbitofrontal areas, or they may occur independently from ischemic events as a result of chronic CADASIL-related white matter changes. Additionally, the relatively early onset of this symptom means that olfactory identification testing may be useful for early evaluation of frontemporal compromise in CADASIL patients. Our report amplifies the literature describing both the spectrum of symptomatology in CADASIL and the geographic spread of the disease.

Contributors

AV, MI, KM and MC contributed equally to the acquisition of the necessary data for drafting this paper. MC and AV were responsible for conceptualization of the paper. All authors were responsible for drafting and editing the manuscript.

Conflicts of interest

We have no conflicts of interest to report.

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