The Journal of Laryngology & Otology
February 2005, Vol. **119,** pp. 148–151

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) presenting with sudden sensorineural hearing loss

John S Phillips, BSc(Hons), MBBS, MRCS(Eng), Jacquelyn A King, MSc*, Siddharthan Chandran, MRCP, PhD†, Peter R Prinsley, FRCS, David Dick, FRCP‡

Abstract
CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is an autosomal dominant angiopathy characterized by recurrent cerebrovascular events, migraine and dementia. We describe a case of sensorineural hearing loss as the presenting feature of this condition. We have found no previous reports in the world literature of CADASIL presenting with a sudden sensorineural hearing loss. The significance of questioning a patient with regard to family history is exemplified in this case.

Key words: Hearing Loss; Sensorineural; Dementia, Multi-infarct

Introduction

Sudden sensorineural hearing loss (SNHL) is as clinically challenging to manage for the ENT surgeon as it is devastating to the patient; 85 to 90 per cent of patients never discover the cause of their hearing loss.[1] We describe the first case of sudden SNHL as a result of an inherited neurological condition called cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Case report

A 42-year-old male sales manager presented to the ENT clinic in July 1997 with sudden, profound, unilateral right-sided SNHL (Figure 1). Past medical history was unremarkable other than revealing a 15-year history of smoking 10 cigarettes a day. Clinical examination revealed no otological abnormalities. Following normal magnetic resonance imaging of the internal acoustic meatus (IAMs) he was discharged with a diagnosis of idiopathic SNHL. He re-presented to the ENT department in December 2002 complaining of progressive hearing loss over the preceding 12 months, this time affecting the left ear (Figure 2). In addition, he reported four episodes of slurred speech associated with lower left facial drop and a left hemisensory and motor deficit over the preceding week. Each episode resolved completely within 12 hours. Examination revealed no otological or neurological abnormalities; he was normotensive. Further questioning on this occasion elicited a family history of genetically confirmed combined autosomal dominant arteriopathy: CADASIL (Figure 3). Investigations including electrocardiography, transthoracic echocardiography and carotid Doppler ultrasonography, along with routine blood tests including cholesterol and a random serum glucose measurement, were unremarkable. An autoantibody screen for rheumatoid factor, antinuclear antibody (ANA), anti-extractable nuclear antibody (anti-ENA), anti-deoxyribonucleic acid (anti-DNA) and anti-neutrophil cytoplasmic antibody (ANCA) was negative. Magnetic resonance imaging of the brain was abnormal: widespread

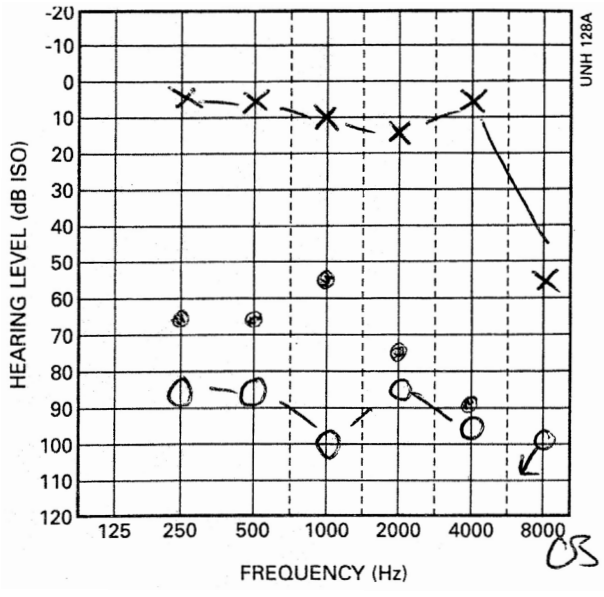

Fig. 1
Pure tone audiogram, July 1997.

From the Departments of Otolaryngology, Audiology* and Neurology‡, Norfolk and Norwich University Hospital, Norwich, UK, and Cambridge Centre for Brain Repair†, Cambridge, UK.
Accepted for publication: 8 November 2004.

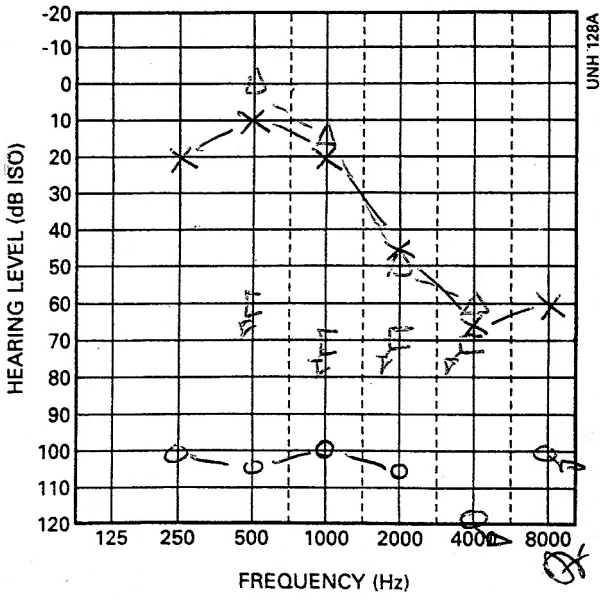

FIG. 2
Pure tone audiogram, December 2002.

high-signal white matter change with prominent involvement of the temporal lobes (Figure 4). The clinical diagnosis of CADASIL was confirmed by genotyping, which identified mutations in exons 3 and 4 of the Notch3 gene. The patient was started on aspirin and had no further transient neurological events over the following six months.

Further audiological assessment

In October and November 2003 further assessment took place to determine the nature and origin of the hearing loss. Pure tone audiometry indicated a moderate high-frequency SNHL on the left and severe-profound SNHL on the right, and showed hearing to be relatively unchanged since December 2002. Tympanometry and otoscopy were unremarkable, and the patient had no clinical signs of facial nerve dysfunction.

Auditory brainstem response testing was performed at 80 dBnHL on the left, and at a maximum output of 90 dBnHL on the right. Clear and repeatable responses were obtained on the left, with the J1-5 latency being within normal limits, hence giving no indication of a retrocochlear pathology. Responses were absent on the right but, given the severity of the hearing loss, it would be unlikely that a response could be elicited from a signal intensity of 90 dBnHL. Otoacoustic emissions were absent bilaterally, indicating impaired cochlear function. Stimulating the right ear, an acoustic reflex was observed with ipsilateral recording at 110, but no reflexes could be measured recording contralaterally. While stimulating the left ear, no responses could be recorded ipsilaterally, but normal responses could be recorded at all frequencies when recording contralaterally. These results suggest that the VIIIth nerve was functional on the left and the VIIth nerve was functional on the right. They also indicate that there was no deficit in the transfer of auditory information at the level of the cochlear nuclei. Considering that tympanometric and otoscopic examination was grossly normal, the likely cause of absence of acoustic reflexes recorded from the left ear was abnormal facial nerve function.

In summary, testing indicated that there was impaired cochlear function on the left, but that it was not possible to determine whether the hearing loss on the right was due to a profound cochlear loss or VIIIth nerve/cochlear nuclei loss with retrograde degeneration resulting in absent otoacoustic emissions. Acoustic reflex testing also indicated impaired VIIth nerve function on the left side.

Discussion

Sudden SNHL may be defined as a loss of 30 dB or more over at least three contiguous audiometric frequencies that develops over a period of a few hours to three days.[2] The estimated yearly incidence is five to 20 cases per 100 000 persons.[3] Idiopathic SNHL is a diagnosis of exclusion that requires cochlear, retrocochlear and central nervous system aetiologies of sudden SNHL to be considered.[4] In 1997 when our case first presented, a diagnosis of idiopathic SNHL was made; five years later the patient was diagnosed with CADASIL. In retrospect the hearing loss may have been the first symptom of this disorder. This is not unusual as SNHL has been reported as the first manifestation of other forms of systemic disease, particularly autoimmune diseases such as Cogan's syndrome,[5] temporal arteritis,[6] Wegner's granulomatosis,[7] polyarteritis nodosa[8] and systemic lupus erythematosus.[9] Neurological conditions such as Dandy-Walker syndrome[10] and Charcot-Marie-Tooth disease[11] have been described as presenting with SNHL. Kirikae *et al.* describe the case of a patient with Buerger's disease (thromboangiitis obliterans cerebri)

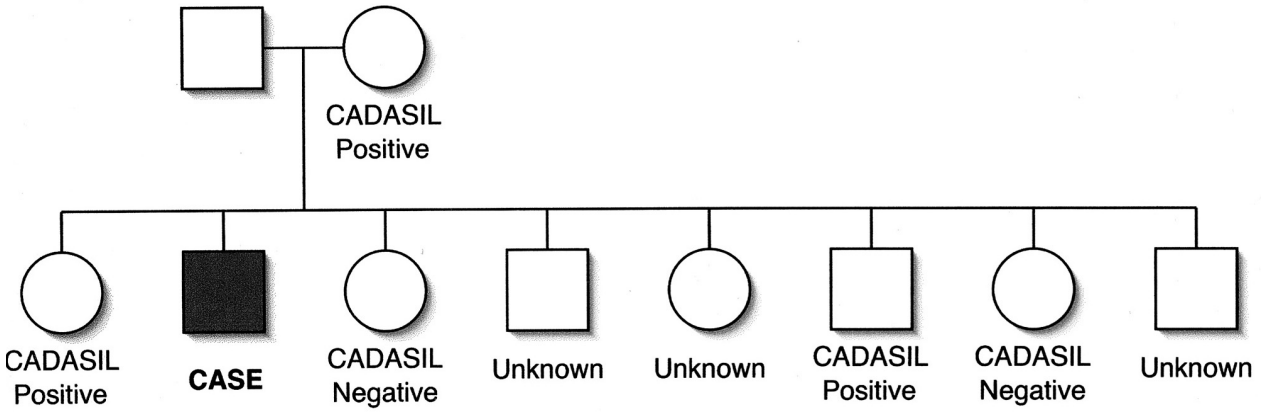

FIG. 3
Family tree demonstrating family members with CADASIL.

https://doi.org/10.1258/0022215053419880 Published online by Cambridge University Press

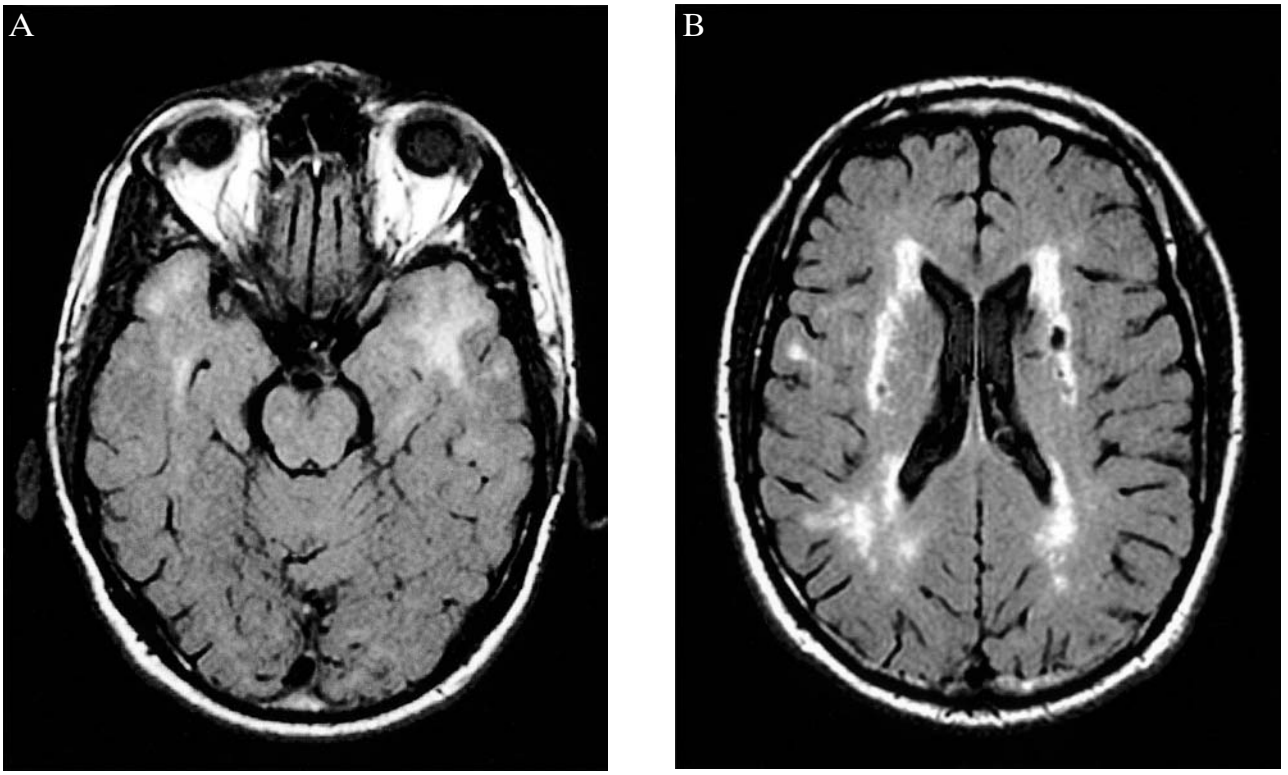

FIG. 4

Magnetic resonance images demonstrating the radiological features of CADASIL. An increased high-intensity T2 signal is demonstrated within (a) the cortical white matter of both anterior temporal lobes and (b) peri-ventricular white matter.

who after developing intermittent claudication noted hearing loss on the same side.[12] Our case bears similarities to a case of sudden cochlear hearing loss due to a saccular aneurysm arising from a loop of the anterior cerebellar artery.[13] In this case an initial computed tomography scan showed no abnormality, but subsequent scanning many months later demonstrated radiological changes not initially evident.

CADASIL, also known as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, is an inherited autosomal dominant condition characterized clinically by dementia, recurrent stroke and migraine. It is caused by mutations in the Notch3 gene and is pathologically characterized by a multi-organ non-atherosclerotic, amyloid negative angiopathy. Ultrastructural finding of osmiophilic material is pathognomonic and together with vascular smooth muscle degeneration results in luminal narrowing of small arteries and arterioles.[14,15] The disease has a progressive or stepwise course with age at onset in the 40s and a mean duration of 13 +/-10 years.[16] Death often occurs in the 50s with a characteristic condition associating a pseudobulbar syndrome and subcortical dementia.[12] The radiological features of CADASIL are typically symmetrical and extensive hyperintense signals within the periventricular and subcortical white matter in T1-weighted images, and hypointense signals of infarctions in the deep white matter and basal ganglia in T2-weighted images.[17,18] Diagnosis is confirmed by identification of the Notch3 gene mutation.

A recent review identified transient ischaemic attack or stroke as the most common presentation of CADASIL, occurring in 43 per cent of patients as compared to 40 per cent with migraine and 15 per cent with cognitive or depressive symptoms.[19] Epilepsy as the presenting feature was reported in 3 per cent of CADASIL cases. Case reports or small series also identify acute encephalopathy,[20] spinal infarct and raised intracranial pressure (ICP) as presenting features of this condition.[21] Ischaemic infarcts, however, are often 'silent' and thought to contribute eventually to gradual disability and cognitive decline. Strokes involving the territory of a large artery have occasionally been reported.[22] In general, CADASIL is a systemic small-vessel arteriopathy with its clinical manifestations being confined to the central nervous system.[23,24] In our patient, the combination of absent otoacoustic emissions and normal brainstem-evoked responses on the left point to impaired cochlear function, whilst on the right it is not possible to determine whether there is a profound cochlear loss, or VIIIth nerve/cochlear nuclei loss with retrograde degeneration resulting in absent otoacoustic emissions. In the context of the later diagnosis of CADASIL, it is possible that the cause of sudden hearing loss was vascular in origin. The labyrinthine artery is often particularly vulnerable and has

TABLE I

ACOUSTIC REFLEX THRESHOLDS

Stimulus	Right ear				Left ear			
Frequency	500 Hz	1kHz	2 kHz	4 kHz	500 Hz	1 kHz	2 kHz	4 kHz
Ipsilateral recording	110	NR	NR	NR	NR	NR	NR	NR
Contralateral recording	NR	NR	NR	NR	90	90	90	105

NR = not recordable

https://doi.org/10.1258/0022215053419880 Published online by Cambridge University Press

been implicated in other conditions resulting in acute SNHL.[25] It is possible that our case suffered an idiopathic sudden SNHL five years earlier, in 1997, and at a later date began to develop the manifestations of CADASIL. The pattern of progressive auditory decline on second presentation is certainly more in keeping with the other clinical characteristics of CADASIL. Although CADASIL cannot be definitely linked to auditory dysfunction in this patient, clinical otolaryngological and neurological as well as laboratory tests have excluded other possible causes for the patient's sudden SNHL. The significance of the impaired facial nerve function is uncertain, but may well be the result of repeated ischaemic episodes.

- **CADASIL is an autosomal dominant angiopathy characterized by multi-infarct dementia**
- **Previous series have confirmed sensorineural deafness as an age-related complication of CADASIL**
- **This is the first report of sudden SNHL in association with this condition**

A large case series of over 100 patients with confirmed CADASIL identified SNHL as an age-related complication of the condition.[21] Our case is unusual as it is the first report of presentation of CADASIL with sudden SNHL. CADASIL as an aetiology for the hearing loss would not have been concluded if it were not for his associated neurological symptoms upon second presentation. Taking a family history is of great significance when assessing a patient with sudden hearing loss; earlier identification of such a history in our case might have expedited diagnosis.

References

1 Mattox DE, Lyles CA. Idiopathic sudden sensorineural hearing loss. *Am J Otol* 1989;**10**:242–7
2 Wilson WR, Byl FM, Laird N. The efficacy of steroids in the treatment of idiopathic sudden hearing loss. A double-blind clinical study. *Arch Otolaryngol* 1980;**106**:772–6
3 Byl FM Jr. Sudden hearing loss: eight years' experience and suggested prognostic table. *Laryngoscope* 1984;**94**:647–61
4 Garcia Berrocal JR, Ramirez-Camacho R. Sudden sensorineural hearing loss: supporting the immunologic theory. *Ann Otol Rhinol Laryngol* 2002;**111**:989–997
5 Garcia Berrocal JR, Vargas JA, Vaquero M, Ramon y Cajal S, Ramfrez Camacho RA. Cogan's syndrome: an oculo-audiovestibular disease. *Postgrad Med J* 1999;**75**:262–4
6 Wolfovitz E, Levy Y, Brook JG. Sudden deafness in a patient with temporal arteritis. *J Rheumatol* 1987;**14**:384–5
7 Kempf HG. Ear involvement in Wegner's granulomatosis. *Clin Otolaryngol* 1989;**14**:451–6
8 Rowe-Jones JM, Macallan DC, Sorooshian M. Polyarteritis nodosa presenting as bilateral sudden onset cochleo-vestibular failure in a young woman. *J Laryngol Otol* 1990;**104**:562–4
9 Bowman CA, Linthicum FH Jr, Nelson RA, Mikami K, Quismorio F. Sensorineural hearing loss associated with systemic lupus erythematosus. *Otolaryngol Head Neck Surg* 1986;**94**:197–204
10 Freeman SRM, Jones PH. Old age presentation of the Dandy-Walker syndrome associated with unilateral sudden sensorineural deafness and vertigo. *J Laryngol Otol* 2002;**116**:127–31
11 Papadakis CE, Hajiioannou JK, Kyrmizakis DE, Bizakis JG. Bilateral sudden sensorineural hearing loss caused by Charcot-Marie-Tooth disease. *J Laryngol Otol* 2003;**117**:399–401
12 Kirikae I, Nomura Y, Shitara T, Kobayashi T. Sudden deafness due to Buerger's disease. *Arch Otolaryngol* 1962;**75**:502–5
13 Rinehart R, Harre RG, Roski RA, Dolan KD. Aneurysm of the anterior inferior cerebellar artery producing hearing loss. *Ann Otol Rhinol Laryngol* 1992;**101**:705–6
14 Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, *et al*. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* 1996;**383**:707–10
15 Ruchoux MM, Guerouaou D, Vandenhaute B, Pruvo JP, Vermersch P, Leys D. Systemic vascular smooth muscle cell impairment in cerebral autosomal dominant arteriopathy with subcortical infarcts and leuckoencephalopathy. *Acta Neuropathol (Berl)* 1995;**89**:500–12
16 Utku U, Celik Y, Uyguner O, Yuksel-Apak M, Wollnik B. CADASIL syndrome in a large Turkish kindred caused by the R90C mutation in the Notch3 receptor. *Eur J Neurol* 2002;**9**:23–8
17 Chabriat H, Levy C, Taillia H, Iba-Zizen MT, Vahedi K, Joutel A, *et al*. Patterns of MRI lesions in CADASIL. *Neurology* 1998;**54**:1869–71
18 Chawda SJ, De Lange RP, Hourihan MD, Halpin SF, St. Clair D. Diagnosing CADASIL using MRI: evidence from families with known mutations of Notch3 gene. *Neuroradiology* 2000;**42**:249–55
19 Desmond DW, Moroney JT, Lynch T, Chan S, Chin SS, Mohr JP. The natural history of CADASIL: a pooled analysis of previously published cases. *Stroke* 1999;**30**:1230–3
20 Schon F, Martin RJ, Prevett M, Clough C, Enevoldson TP, Markus HS. "CADASIL coma": an underdiagnosed acute encephalopathy. *J Neurol Neurosurg Psychiatry* 2003;**74**:249–52
21 Dichgans M, Mayer M, Uttner I, Bruning R, Muller-Hocker J, Rungger G, *et al*. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Ann Neurol* 1998;**44**:731–9
22 Rubio A, Rifkin D, Powers JM, Patel U, Stewart J, Faust P, *et al*. Phenotypic variability of CADASIL and novel morphologic findings. *Acta Neuropathol (Berl)* 1997;**94**:247–54
23 Rouchoux MM, Maurage CA: CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *J Neuropathol Exp Neurol* 1997;**56**:947–64
24 LaPoint S, Patel V, Rubio A. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). *Adv Anat Pathol* 2000;**7**:307–21
25 Chae SW, Cho JH, Lee JH, Kang HJ, Hwang SJ. Sudden hearing loss in chronic myelogenous leukaemia implicating the hyperviscosity syndrome. *J Laryngol Otol* 2002;**116**:291–93

Address for correspondence:
Mr John S Phillips,
Senior House Officer,
59 Eade Road,
Norwich NR3 3EH, UK.

E-Mail: john.phillips@mac.com

Mr J S Phillips takes responsibility for the integrity of the content of the paper.
Competing interests: None declared