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A case of late-onset CADASIL with interhemispheric disconnection features

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Sirs: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a recently discovered inherited disorder that usually leads to cerebrovascular manifestations in mid-adulthood [9]. We report a late-onset sporadic case of genetically proven CADASIL with an atypical pattern of progressive cognitive deterioration.

A 61-year-old right-handed male was referred with a five-year history of progressive neurological decline characterized by apathy, cognitive impairment, gait difficulties and urinary incontinence. He reported no history of migraine and had no cerebrovascular risk factor including high blood pressure. Family history was negative for migraine, stroke, dementing illness or epilepsy. His father died at age 90 from heart disease. His mother had suffered from an unspecified gait disorder and died at age 82 from a non-neurological cause. The patient had no siblings and was the father of a healthy 37 year-old woman. Clinical symptoms had begun 5 years before with cognitive slowing and personality changes marked by decreased interest and depression. Two years later, he was noted to have attentional difficulties, depressed mood and slight gait slowing. On neurological examination, gait was slow and unsteady. He showed mild facial and limb hypokinesia but no rigidity. Reflexes were brisk in upper and lower limbs, and cutaneous plantar responses were flexor. A global intellectual deterioration was observed (WAIS-R IQ: 69 with performance IQ: 57 and verbal IQ: 79) [11]. Detailed neuropsychological assessment (Table 1) revealed preserved episodic memory, attentional and executive functioning impairment and the presence of interhemispheric disconnection features. Examination of upper limbs ideomotor praxis revealed marked left hand impairment, while gestures were adequately performed with his right hand. He displayed left hand agraphia, which was characterized by scrawl or no response. Tactile naming of objects placed in his left hand was severely impaired and dichotic listening showed complete left ear extinction.

Cranial MRI was performed with a 1.5 T unit (Siemens Magnetom Symphony). Images covered the whole brain and were obtained in the coronal plane for T1, T2 and FLAIR, and also in the sagittal plane for T1. Images were reviewed by two neurologists unaware of the clinical findings. Lesions equivalent to the signal characteristics of cerebrospinal fluid (CSF) on T1-weighted images and > 3 mm in diameter, as well as wedge-shaped corticosubcortical lesions, were regarded as brain infarcts [6]. Brain MRI revealed no infarcts as had been suggested, in particular in the basal ganglia-thalami region. It showed diffuse, symmetric and confluent white matter hypersignals on T2-weighted images, contrasting with mild signal abnormalities on T1 images. The temporal poles were relatively spared, and the corpus callosum appeared abnormally thin. Diffuse cortical and subcortical atrophy was also evident (Fig. 1).

Laboratory evaluation showed a normal chemistry survey, complete blood count, sedimentation rate, fibrinogen level, C-reactive protein, serum protein and lipoprotein electrophoresis, thyroid function tests, vitamin B12, folates and urinalysis. Human immunodeficiency virus, TPHA and VDRL testings,

Table 1 Main neuropsychological results

Neuropsychological Assessment	Raw score (clinical significance)
General assessment	
WAIS-R, full score	69 (mild)
Verbal IQ	79 (moderate)
Performance IQ	57 (severe)
MMSE	17/30 (moderate)
Digit span (forward; backward)	4; 2 (severe)
Lexical verbal fluency (p)	16 (2 min., mild)
Category verbal fluency (animals)	10 (2 min., severe)
Logical memory subtest of the WMS-R	20 (normal)
Boston Naming Test	53/60 (mild)
Interhemispheric tasks	
Ideomotor praxis: LH; RH	0/10 (severe); 10/10 (normal)
Tactile naming of objects: LH; RH	2/10 (severe); 10/10 (normal)
Dichotic listening: LE; RE	0/50; 50/50 (full left ear extinction)

MMSE Mini-Mental State Examination; *WMS-R* Wechsler Memory Scale-Revised; *WAIS-R* Wechsler Adult Intelligence Scale Revised; *LH* left hand; *RH* right hand; *LE* left ear; *RE* right ear

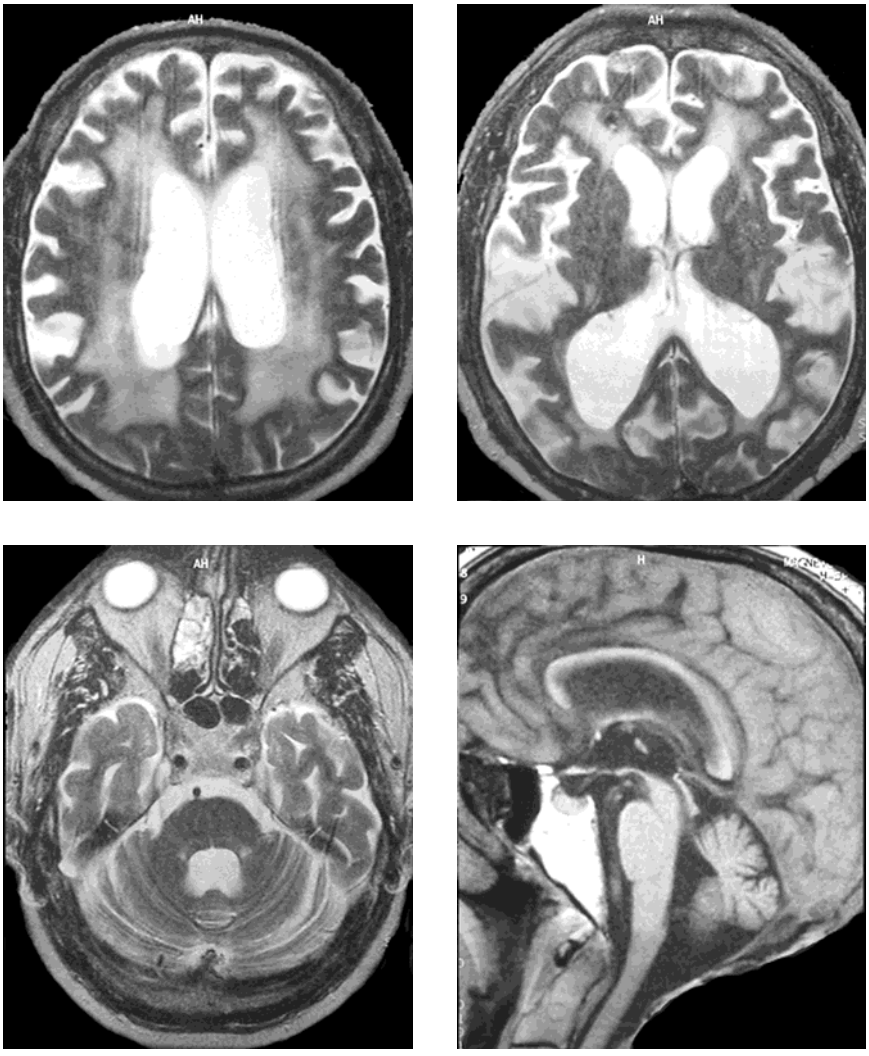

Fig. 1 Brain MRI performed 5 years after clinical onset. Cut at the level of the lateral ventricles (left upper view) and the basal ganglia-thalami region (right upper view). The T2 weighted axial MRI shows severe ventricular enlargement, moderate cortical atrophy, confluent symmetrical high signals in the white matter and no multiple and/or strategically located infarcts. In contrast, the temporal poles appear relatively spared (left lower view). Note the decreased size of the corpus callosum on the T1 weighted mid-sagittal section (right lower view)

and screening for lysosomal and peroxisomal disorders were all negative. Lumbar CSF analysis showed slight protein level elevation (640 mg/l) and no oligoclonal band. CSF cytology, stains and culture were negative. A brain biopsy had been undertaken at age 59 in the white matter of the right frontal lobe. It revealed vascular hyalinization causing arteriolar narrowing, and white matter pallor with no active demyelination. Genetic analysis showed a missense mutation resulting in the substitution of a C for a T at nucleotide position 697 within exon 4 of the notch 3 region of chromosome 19p13.1 (replacement of an arginine for a cysteine residue at amino-acid position 207). This is typical of CADASIL and has not been observed in a panel of 200 control chromosomes [5].

Dementia is the second commonest clinical symptom in CADASIL and is present in up to 90 % of patients before death [2, 3]. Although early cognitive symptoms are frequently of subcortical type with prominent frontal lobe features [8], the pattern of impairment at the established state of the disease is heterogeneous [3]. Evolution of neuropsychological impairment is generally progressive with additional stepwise deterioration. In a minority of patients, cognitive decline may be strictly progressive mimicking the course of a degenerative disease. However, conventional neuroimaging studies performed on these subjects disclose strokes, in particular in basal ganglia regions [1, 4, 10].

The patient described here exhibited several atypical features. First, no clear family history was found among the first-degree relatives. Second, evidence of clinical and radiological macroscopic infarcts was lacking. Third, he presented with an atypical pattern of slowly progressive cognitive deterioration. In addition to executive functions impairment, the patient also presented with a posterior interhemispheric disconnection syndrome which was associated left ideomotor apraxia, left hand tactile anomia, left hand agraphia and left ear extinction on dichotic listening. Callosal infarcts are not uncommon in CADASIL [7], although they were not observed here. Brain MRI essentially disclosed callosal atrophy, suggesting that interhemispheric disconnection symptoms were likely to reflect an insult of transcallosal fibers in their intrahemispheric route. Sporadic small vessel disease may also result in decreased size of corpus callosum, but the presence of callosal symptoms is unusual in this setting [12]. Finally, the present cognitive pattern that associates inter-hemispheric disconnection features and intact episodic memory do not support a superimposed degenerative condition such as Alzheimer's disease.

This observation suggests that ultrastructural examination of pe-

ripheral tissue samples and further molecular analysis for CADASIL should be considered in presence of sporadic cognitive decline and extensive white matter lesions of unknown etiology, especially when significant cerebrovascular risk factors are lacking.

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