

## Case report

# CADASIL: underdiagnosed in psychiatric patients?

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**Objective:** Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is exclusively related to symptoms of the central nervous system. Retrospectively in up to 15% the initial presentation is psychiatric disturbances. In these cases the diagnosis often is delayed or missed.

**Method:** Two cases of CADASIL diagnosed in a psychiatric hospital are presented.

**Results:** Both patients were admitted to the gerontopsychiatric department (one because of a suicidal attempt and a depressive episode, the other because of cognitive decline and progressive personal neglect). Brain magnetic resonance imaging (MRI) showed severe leukoencephalopathy in the absence of cardiovascular risk factors. In both cases, diagnosis of CADASIL was made by the identification of specific granular osmiophilic material in skin biopsies.

**Conclusion:** Brain MRI should be performed in all cases of late onset of severe psychiatric symptoms. CADASIL should be considered as a possible differential diagnosis whenever a marked leukoencephalopathy is detectable. Diagnosis can be verified by taking a skin biopsy or by specific genetic testing.

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Key words: CADASIL; psychiatric disturbances; mood disorder; depression; cognitive impairment; dementia

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## Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary disease causing typical histopathologic alterations, namely the deposition of specific granular osmiophilic material (GOM) between degenerating smooth muscle cells, which can be detected in the walls of medium-sized and small arteries of virtually all organs (1). In contrast, clinical manifestations of CADASIL are nearly exclusively related to the central nervous system: recurrent transient ischemic attacks (TIA), stroke-like episodes or stroke, migraine and cognitive decline (2, 3). The disease manifestation lies between the third and sixth decade. Brain magnetic resonance imaging (MRI) reveals diffuse areas of hyperintensities of the white matter predominantly located subcortically. Further, lacunar infarcts, microbleeds and subcortical lacunar lesions are observed (4). The radiologic abnormalities are already detectable in asymptomatic individuals (5).

Temporal pole hyperintensities and involvement of the external capsule may help to distinguish patients with CADASIL from subcortical arteriosclerotic encephalopathy (6). The diagnosis is made by genetic testing or by skin biopsy (7).

In addition to the clinical presentations mentioned above, a variety of psychiatric disturbances can occur in CADASIL. Affective and adjustment disorders are mainly observed, but also agoraphobia, addiction to alcohol and psychotic pictures were described (2, 3, 8, 9). Retrospective studies found that depressive episodes are not uncommonly the initial symptom of the disease (10). Further, cognitive decline is accompanied by the frontal lobe functions being affected and patients have impaired executive and organizing abilities, slowing of mental abilities, poor concentration or slowing of motor functions while memory disturbances are less prominent (1). This presentation of symptoms often leads to the diagnosis of a mood disorder.

While transitory ischemic attacks or strokes will always prompt neuroimaging, psychiatric distur-

bances rarely indicate brain imaging procedures. Therefore the diagnosis of CADASIL is often delayed or missed. We present two cases of our gerontopsychiatric department and propose criteria when this presumably underdiagnosed disease should be taken into consideration.

### Case reports

#### Case 1

A 66-year-old retired painter was admitted to our gerontopsychiatric day hospital in November 2003 because of mood instability and a slowly progressive memory impairment. The relatives reported that first psychic changes began around 1996. In his premorbid personality, the patient was described as reserved, peaceful and calm. During the last years he started to neglect himself and his duties, became more easily irritable and often lost control about his behaviour. Disorganization affected his private and professional life. In 1997 a submanic syndrome was diagnosed by an out-patient psychiatrist and a neuroleptic drug prescribed. His condition improved mildly. In the following course the patient began to consume alcohol again after 4 years of abstinence. The family doctor prompted an MRI of the brain in 2001 that revealed a considerable subcortical leukoencephalopathy. No history of high blood pressure was notable. After withdrawal from alcohol again in summer 2003 the psychic changes and cognitive impairment deteriorated further.

The father of the patient had died at 74 years of age after having three strokes accompanied by progressive dementia. He had diabetes and arterial hypertension. In contrast, a history of smoking was the only vascular risk factor in our patient. He had no siblings. His daughter suffered from migraine attacks while his sons were healthy.

On admission the patient was digressive with slightly increased impulse and diminished distance. Formal thinking was a little desultory. He had no delusions and his orientation was intact. Neuropsychological testing showed impaired executive functions, reduced attention and deficits in declarative and working memory. Medical and neurological examination was without pathologic finding.

The MRI of the brain showed a severe confluent leukoencephalopathy with single lacunar infarcts and microbleedings in the basal ganglia (Fig. 1). In the diffusion-weighted image two small fresh lesions were noted. Positron emission tomography showed unspecific metabolic changes of the brain. EEG was normal.

Extensive workup of blood samples and clinical chemistry were unremarkable, especially with

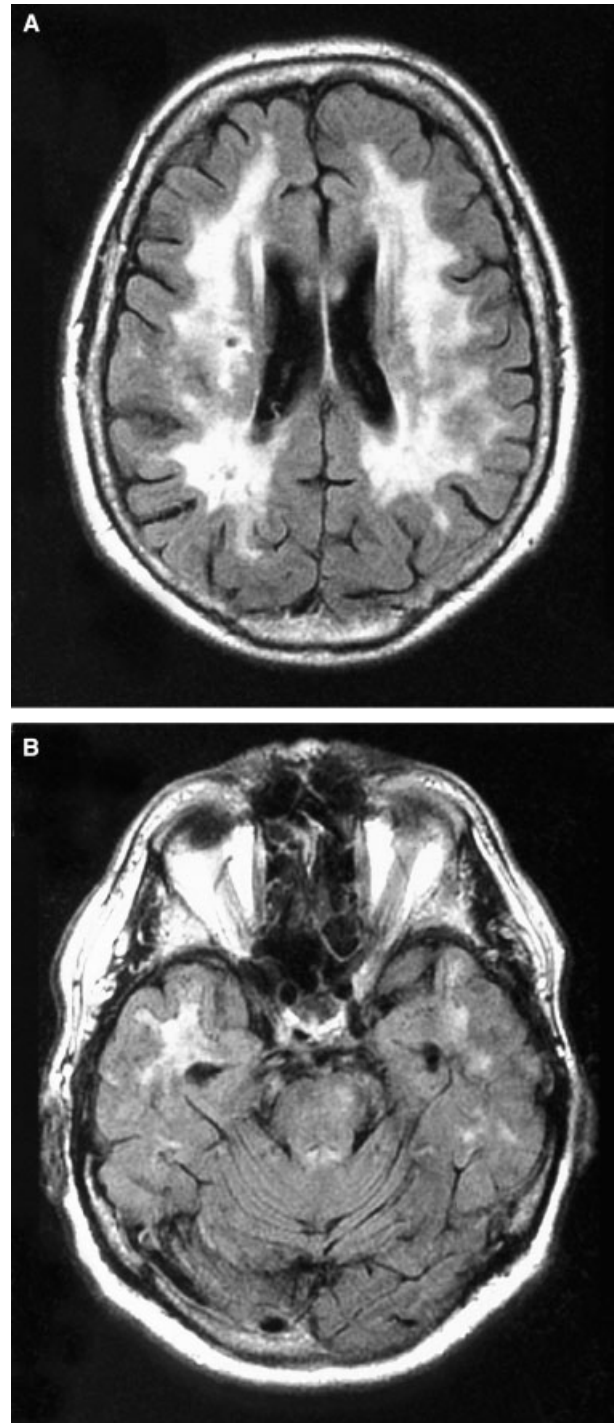


Fig. 1. Transversal orientated FLAIR sequence brain MRI of patient 1. Severe leukoencephalopathy involves almost the complete white matter (a). Of note, white matter lesions are found also in the temporal poles (b).

regard to metabolic, infectious or immunological parameters.

Cerebrospinal fluid parameters including cell count, IgG index, oligoclonal bands, tau-protein, beta-amyloid 1-42, protein 14-3-3, neuron-specific

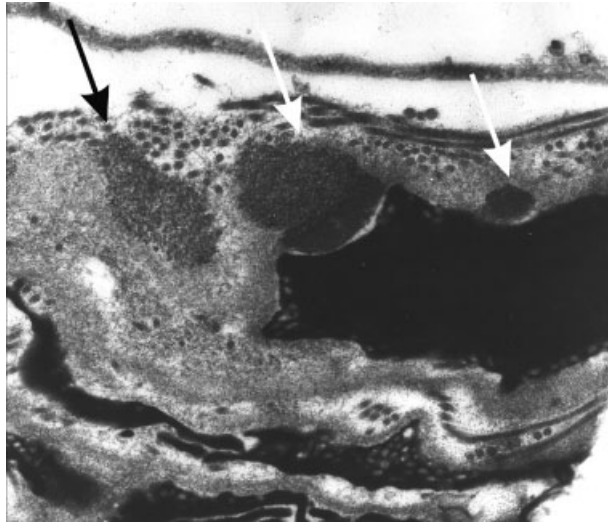


Fig. 2. Electron microscopy reveals typical granular osmophilic material (arrows) in the skin biopsy of patient 1.

enolase as well as bacteriological and virological examinations were all normal.

Ophthalmological examination revealed marked microvascular changes at the fundus of the eye which were initially thought to be typical for changes caused by arterial hypertension. However, the blood pressure of the patient was always normal.

Finally a skin biopsy was taken and revealed the pathognomonic GOM that were identified by electron microscopy (Fig. 2). This led to the diagnosis of CADASIL.

A low potent neuroleptic (Dipiperone) was prescribed to decrease the patients impulsivity. An admission to a day care unit was organized.

#### Case 2

A 63-year-old woman was admitted to a psychiatric hospital in summer 2003 because of a suicide attempt. The otherwise healthy woman had a 2-year history of depressive symptoms, which were covered by a psychiatric practitioner and successfully treated with amitriptyline. During several weeks prior to admission the depressive symptoms deteriorated despite medication and were accompanied by paranoid ideas in the sense of pauperization and larceny delusions. There was no history of prior neurological or psychiatric symptoms and no relevant antecedent or concomitant medical disorders or life events were reported by the patient. Psychopathologically she was regressive and melancholic. Neurological examination was unremarkable except for a bound gait and a mild polyneuropathy.

Social and family history revealed that the patient was married and retired. She had two sons. Both already had psychiatric symptoms requiring hospital admissions, one because of depression, the other because of addiction problems at 16–20 years of age. The patient had no siblings and her parents had died at old age without suffering of strokes and dementia.

She received antidepressive, neuroleptic and anxiolytic medication. However, she continuously deteriorated within the next 6 weeks becoming more and more mutistic and inactive. An impressive slowing of her speech and activity sequences were noticed. Further, she developed intermittent loss of her bladder control. Clinical chemistry and other laboratory parameters were unremarkable.

Brain MRI was performed and revealed a severe leukoencephalopathy. No cardiovascular risk factors could be detected, there was no history of prior ischemic attacks or stroke-like episodes.

The patient was referred to the neurological university hospital where she attempted a second suicide and therefore was immediately transferred to the psychiatric university hospital. Here neurological and psychopathological status was as described above. Noteworthy, the mutistic appearance was accompanied by a distinct visuoconstructive apraxia. Accordingly, neuropsychological testings basically showed normal values in memory testings (MMSE 28/30) and cognitive abilities (HAWIE 110 points). Significant deficits however were noticeable in her visuoconstructive abilities, either concerning daily life activities or formal test challenges.

An extensive diagnostic workup was initiated in order to classify the leukoencephalopathic picture. Electrophysiological examinations showed delayed sensory evoked potentials of the tibial nerve. However, basically all blood parameters, clinical chemistry and laboratory markers were within normal range. Further, CSF analysis was unremarkable. All metabolic, infectious or immunological parameters tested as possible differential diagnosis of leukoencephalopathies were negative. Finally a skin biopsy was performed showing typical osmophilic deposits (GOM) pathognomonic for CADASIL.

In the course, the psychopathological symptoms slowly improved under a combination of antidepressive (Reboxetine), anxiolytic (Tavor) and neuroleptic (Risperidone) medication. Neuropsychological symptoms remained unchanged although considerable fluctuations on a day-by-day basis were noticeable. The patient could be dismissed at home after approximately 3 months in the psychiatric department.

## Discussion

CADASIL is caused by mutations within the Notch3 gene on chromosome 19 which has 33 exons and encodes a Notch3 receptor protein of 2321 amino acids with a single transmembrane domain (11). It is a member of the Notch family, which in mammals has four members and plays a pivotal role during development. In contrast, the exact function of Notch3 in adult animals, in which it is exclusively expressed in vascular smooth muscle cells, is unknown (12).

More than 95% of the described CADASIL cases to date are the result of missense point mutations in the extracellular domain of Notch3. In approximately 70% of the patients these mutations are located within exons 3 and 4. In addition to that, four different small deletions have been described. Nearly all mutations result in a change from an even to an uneven number of cysteins in the extracellular domain of Notch3. It is speculated that these alterations affect the formation of sulfur bridges and thereby the three-dimensional structure of this domain leading to defective signaling in the vascular smooth muscle cells eventually causing their degeneration. As CADASIL is an autosomally dominant inherited disease, both alternatives, haploinsufficiency (i.e. one wild type allele of Notch3 not being sufficient to maintain normal cellular function) and toxic gain of function, are plausible. The pathologic process causes a progressive thickening of the walls of small and medium-sized arteries thereby reducing the arterial lumen. This process is carried out systemically. The predominant affection of the white and deep gray matter of the brain can be explained by the fact that these areas are supplied by relatively long penetrating arteries of the end artery type without efficient collateral connections to the neighboring arteries (1).

CADASIL demonstrates wide interfamilial and intrafamilial variation regarding age of onset, clinical symptoms and course of the disease. Even in monozygotic twins tremendous differences in the clinical picture were described (13).

Crucial for the suspicion of CADASIL is MRI of the brain revealing prominent signal abnormalities in the subcortical white matter and basal ganglia. Although typical lesion distribution in CADASIL were described (5, 14), the picture is not so pathognomonic that it excludes other possible reasons of leukoencephalopathy. In principle, the differential diagnosis of leukoencephalopathy is broad and must take into account comorbidity factors, laboratory values and metabolic testings.

The diagnostic workup in CADASIL patients with stroke or TIA and leukoencephalopathy without cardiovascular risk factors will soon lead to diagnosis, especially if patients are affected at relatively young age and family history is positive. However, there is a group of up to 15% which presents with psychiatric disturbances as initial symptoms (10). In this cases, the diagnosis of CADASIL will often not be suspected for a long time or completely dismissed.

Case 1 demonstrates that even a first brain MRI already showing prominent leukoencephalopathy in a patient without a history of hypertension did not prompt any further investigations. At that time a sporadic subcortical arteriosclerotic encephalopathy was supposed in the 64-year-old patient. Family history was relatively unspecific with the father dying after several strokes but having diabetes and arterial hypertension and a daughter suffering by migraine attacks. Moreover the change of character beginning in the age of 59 was first interpreted as submanic syndrome and not as frontal lobe dysfunction which probably would have forced neuroimaging earlier.

Case 2 illustrates that first the poor response to psychopharmacological treatment and the development of physical symptoms in the patient with late onset depression prompted neuroimaging which by then demonstrated a severe leukoencephalopathy. In the absence of cardiovascular risk factors an extensive diagnostic workup finally led to the diagnosis of CADASIL.

Our cases corroborate the importance of neuroimaging in any case of severe psychiatric symptoms with late onset. Whenever a marked leukoencephalopathy was detected, CADASIL should be taken into consideration as a possible differential diagnosis, especially in cases without vascular risk factors. In younger patients with psychiatric disturbances, a family history of stroke, migraine with aura or dementia should prompt a brain MRI. Detection of white matter lesions especially when involving the anterior temporal lobe are suspicious for CADASIL in these cases (4).

One very important disease component is its inheritance. Second generation offspring of patients have a 50% risk to receive the deleted gene and carrier of the mutation will develop symptoms because of the very high penetrance of the gene mutation. With regard to family planning it is therefore important to aspire to a genetic counseling with the offer of genetic testing.

There is no causal treatment for CADASIL. The disease symptoms fluctuate but the course is nonetheless clearly progressive, sometimes with relapses and distinct remissions. At present only

## Invited comment

symptomatic therapy is available without ensured effect of anticoagulants or antiaggregants for the prevention of TIA or strokes. In slight contrast it seems that psychiatric symptoms in CADASIL patients are quite susceptible to drug therapy, which follow the common recommendations.

Of note, patients with CADASIL are at higher risk of angiographic complications. Therefore cerebral angiography should be avoided wherever possible (15).

In summary our report alludes to CADASIL as a relevant differential diagnosis in the psychiatric clientele. Diagnosis can be established relatively easily by the combination of brain imaging combined with a skin biopsy (or alternatively specific genetic testing). A positive family history is strongly indicative for the initial diagnostic considerations but despite its autosomal dominant inheritance not an essential requirement. Early diagnosis will help to choose appropriate strategies of management and counseling.

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## Invited comment

### Severe brain pathology: Underdiagnosed in psychiatric patients?

Vascular dementia includes cortical vascular dementia related to large vessels, involving cerebral areas critical for higher functions, and subcortical vascular dementia, previously named Binswanger’s disease, related to smaller vessels. The pathogenesis of subcortical vascular dementia remains unknown with heterogeneous causes. However during recent years, a variant of subcortical vascular dementia has been identified: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL. CADASIL is an autosomal dominant inherent angiopathy caused by mutations in the *Notch3* gene on chromosome 19. The disease is characterized clinically by recurrent ischaemic episodes and progressive cognitive deficits but additional manifestations like mood disorders, migraine and epileptic seizures may be prevalent (1). Magnetic resonance imaging (MRI) reveals diffuse hyperintensities of the white matter and other unspecific changes (2). The discovery of granular osmiophilic material in the skin of patients with CADASIL as an easy and pathognomonic diagnostic test initiated a cascade of interest (1). Although 10–15% of patients with CADASIL may present with psychiatric symptoms initially (3), the illness has not attracted much attention in psychiatry. It is not known how prevalent CADASIL is among patients in gerontopsychiatric or neuropsychiatric units but the two cases initially presenting with affective symptoms,