Cerebral Circulation - Cognition and Behavior 3 (2022) 100043

Contents lists available at ScienceDirect

Cerebral Circulation - Cognition and Behavior

journal homepage: www.sciencedirect.com/journal/cerebral-circulation-cognition-and-behavior

Cognition, mood and behavior in CADASIL

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A B S T R A C T

CADASIL is the most common familial cerebral small vessel disease (cSVD). Stereotyped mutations of the NOTCH3 gene are responsible for this archetypal ischemic cSVD that can lead, at the very end stage, to severe dementia. Variable cognitive alterations, mood, or behavior disturbances are frequently observed during the course of the disease. In this review, these clinical manifestations, their occurrence, severity and duration are analyzed in relation to the disease progression. Also, the potential relationships with cerebral lesions and treatment options are discussed.

Introduction

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is the most common hereditary cerebral small vessel disease (cSVD) [1]. The disease is caused by cysteine-altering variants in one of the 34 EGFr domains of the NOTCH3 protein, a receptor expressed at the surface of arteriolar smooth muscle cells and capillary pericytes. The mutant NOTCH3 receptor accumulates in the vascular wall [2] and aggregates with other matrix proteins whose functions are subsequently altered [3,4]. These modifications lead to important changes in the microvasculature resulting in altered neurovascular coupling, decreased hemodynamic response to blood pressure variations and hypoperfusion in the deepest brain areas [5,6]. The precise molecular mechanisms behind these microvascular disturbances are progressively deciphered in preclinical models of the disease [7–9].

While its prevalence was initially estimated from clinical studies to vary between 1 and 5 per 100,000 [10,11], recent genetic investigations in large population-based samples have shown that the frequency of presumably pathogenic cysteine-altering variants in the NOTCH3 gene was much higher than expected and could reach 2–4 in 1000 in the general population [12,13]. The location of these mutations within or outside the EGFr domains 1-6 along the NOTCH3 protein has been shown to play a key role in the disease severity and symptom onset [14] and might explain the discrepancy between clinical and epidemiological studies. Very mild and late-onset forms of the disease, most often associated with variants in EGFr domains 7-34, are therefore quite frequent and a large number of these cases remain undiagnosed [13–15]. Recent studies have also shown that these variants can remain non-penetrant up to at least age 70 years, even on MRI showing only discrete signal changes [16].Vascular risk factors can also modulate the clinical expression of the disease, as well as, most likely, undetermined genetic factors that may explain the large intrafamilial phenotypic variability [17–19].

The cognitive, mood and behavior disturbances in CADASIL are key manifestations of the disease [20,21]. They have been recognized as characteristic phenotypic traits since the first descriptions of the disease even before the identification of the NOTCH3 gene [21–23]. They are important to consider for multiple reasons. At early stage of the disease, even moderate changes in cognitive performances may have a significant impact on the professional activity or quality of life. Later, after the occurrence of stroke events, cognitive decline should not be overlooked. At advanced stages of the disease, there is often severe cognitive impairment, disability and functional dependence. On the other hand, psychiatric symptoms may be inaugural and lead to misdiagnosis or diagnostic delays at the onset of the disease [24,25]. In patients first evaluated by psychiatrists because of mood or behavioral disturbances, the diagnosis is often raised secondarily because of a suggestive family history, MRI abnormalities detected incidentally, or, an unusual response to psychotropic treatments [26]. Also, psychiatric symptoms may be severe enough to lead to patient's hospitalization, isolation of patients from work and/or family [1,27], suicide attempts or considerable disruption to medical management.

Natural history and main clinical features

Since the identification of CADASIL in 1993, thousands of families and case reports have been reported throughout the world describing the most salient clinical and imaging features of the disease [28].

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https://doi.org/10.1016/j.cccb.2022.100043
Received 16 January 2022; Received in revised form 6 February 2022; Accepted 6 February 2022
Available online 9 February 2022

Overall, the global presentation appears to be relatively homogeneous [1,22,29]. Vascular risk factors such as hypertension or smoking were found to accelerate the onset of ischemic events [17,18]. The disease onset is between the age of 20 and 40 years, when cerebral white matter hyperintensities become visible on T2-weighted MRI, in most diagnosed individuals and their NOTCH3 positive family members. The earliest clinical manifestations are attacks of migraine with aura. Migraine with aura is, however, inconsistent and only reported by 30–40% of patients [1,22,29,30]. Aura symptoms are typical or atypical. They can be sometimes extremely severe and some prolonged auras may even be complicated by a severe but regressive encephalopathy leading to agitation, confusion or even coma [31,32]. Attacks of migraine with aura occur earlier in women than in men [30]. In the mid-50s, CADASIL patients usually present with ischemic events, either transient ischemic attacks (TIAs) or completed ischemic stroke. Related focal deficits correspond to typical lacunar syndromes only in 2/3 of cases [22]. These manifestations are related to focal subcortical ischemic lesions and may regress in early stages of the disease. Their repetition can lead, especially after the age of 60 years, to the development of significant cognitive and motor disability that can lead to dementia associated with motor deficits, and gait and balance difficulties [1,22,29].

From the onset up to the terminal stage of the disease, both cognitive and psychiatric manifestations are frequently reported [20]. These may include mood disturbances, particularly mild or severe depressive episodes. Cognitive decline progresses gradually over several decades [33] with symptoms that can range from subtle deficits in executive function at the onset of the disease to profound dementia [34].

Mood disturbances

Mood disturbances occur commonly during the course of CADASIL. However, their frequency differs among patients. Analysis of 13 cohorts described in the literature, each including at least 20 symptomatic CADASIL patients, shows that this frequency may vary from 7 to 50% [10,29,35–44]. Mood disturbances are most often reported between 30 and 60 years of age, in the presence of some cognitive changes, and after the occurrence of the first stroke event [45]. However, in some cases, they can be also inaugural and occur in the absence of any other symptom or cognitive deficit [24].

Mood disturbances are extremely variable in intensity and their clinical presentation also varies widely. About half of symptomatic patients may also suffer from variable degree of emotional disturbances [46]. They can be related to depressive symptoms but also include anger proneness, irritability, excessive or inappropriate laughing or crying outside depressive symptoms [46].

Anxiety or mild depressive episodes are the prominent manifestations. They are sometimes attributed to stressful situations within families [47]. Some contextual aspects related to a severe family disorder may elicit or accelerate the onset of depressive symptoms. The frequency of more severe depression with a potential risk of suicide attempt is increased [48]. Depression has an independent impact on the quality of life of patients [49]. Severe depression, sometimes evoking melancholic or even stuporous states, are also reported [20,50]. They have been experienced by nearly 10% of patients [51]. In the most severe cases, associated symptoms such as anhedonia, paranoid thinking, and alogia have been observed [50]. Panic attacks can also occur [26]. In some cases, physical stiffness with catatonia have been even reported [50].

Conversely, manifestations of exalted mood and excitement are observed less frequently than depression. These may be hypomanic or manic episodes leading to significant behavioral disturbances [52–54]. Euphoria was reported in 8% of 132 symptomatic patients by Reyes et al. [54,]. Some patients have depressive episodes alternating with manic states and have clinical features suggestive of dysthymic or bipolar disorders [53,56,57] Table 1.

Table 1
Main neuropsychiatric and cognitive manifestations in CADASIL.

Mood disturbances	Cognitive alterations	Behavioral disturbances
Anxiety	Reduction of cognitive speed	Irritability
Panic attacks	Attention deficit	Decreased interest in the immediate environment
Depression	Concentration alterations	Reduction of general activities
Melancholia	Reduced mental flexibility	Apathy
Stuporous state	Memory alterations affecting retrieval at onset	Prostration
catatonia		Agitation
Euphoria, exaltation	Global memory deficit affecting encoding at late stage	Confusion
Hypomanic or manic episodes	Moderate up to severe dementia	Angry outbursts
		Acts of violence

Cognitive changes

Cognitive disturbances range from moderate cognitive slowing to impairment of executive functions and may progress to a global decrease of cognitive efficiency up to severe dementia [29,58–61].

At the beginning of the disease, a slowing down of cognitive processes is detected. These changes can remain isolated for several years. At this stage, tests usually show that the objectives proposed in various cognitive tasks are achieved without difficulty, but that timed tasks are carried out significantly slower than in healthy subjects [62]. This slowing down was confirmed in patients who had no global cognitive impairment by using visual stimulation on a screen when measuring their reaction time [62,63].

At the intermediate stage, the cognitive slowdown further increases but altered executive functions are then always detected. More specifically, performances in attention, concentration and/or mental flexibility are significantly reduced. These changes are variable among patients and more or less combined, but they progressively worsen during the course of the disease. They may occur in the absence of modification of global cognitive efficiency. Memory capacities are still relatively preserved. When the verbal Free and Cued Selective Reminding Test is applied, the encoding of information is found preserved, but its retrieval is impaired [64]. For a long time, however, retrieval is facilitated by indices, suggesting that hippocampal functioning is preserved and that memory difficulties are primarily related to some frontal networks dysfunction. At that time, most visuo-constructive and praxis functions are also preserved.

At more advanced stage of the disease, diffuse cognitive changes are detected. Cognitive slow down and executive dysfunction further aggravate, memory difficulties become obvious with both a reduction of encoding and retrieval of information. The diagnostic criteria for dementia can then be met, even in the absence of any previous stroke event [65]. The severity of cognitive impairment is then, often associated with motor impairment which particularly affects gait and balance. Tests measuring walking speed or time to maintain a prolonged monopodial position are highly sensitive to these motor difficulties [66]. At the end stage of disease, the slowing down is extreme, patients are almost mute, they become bedridden and totally dependent on their relatives or other care-givers. This end-stage usually occurs around the age of 70 years, but can be much earlier [1].

Behavioral disturbances

Behavioral changes in CADASIL patients may occur at all stage of the disease, but are often associated with the onset of cognitive alterations. They can be subtle or spectacular but are not always reported by the patient him-or herself. Only gathering information from those closest to the patient allows to discern and identify behavioral changes occurring

during the course of the disease.

Initially, patients or their relatives usually notice personality changes, such as increased irritability, although this is rarely reported spontaneously and should be actively enquired. A decrease in interest and activity is also frequently observed, often progressing to apathy, which is one of the most frequent behavioral manifestations of the disease, Apathy, i.e. a significant reduction in goal-directed behavior, is reported in more than one third of symptomatic individuals [54]. Most often, the diagnosis of apathy is made when close relatives report that their family-member, who was previously a dynamic person, has become inactive, remains prostrate for several hours and does nothing or watches television for hours. These behavioral changes usually are more disturbing for the patient's family than for the patient him-or herself. Apathy has a major and independent impact on the patient's quality of life [54]. It is usually detected in individuals who already have a history of stroke events. It can be present in the absence of depression. Recently, Le Heron et al. showed that apathetic CADASIL patients had a reduced incentivization to reward rather than a hypersensitivity to effort costs [67]. Globally, apathetic patients present with more severe cognitive and motor impairment than nonapathetic individuals [54].

Other behavioral modifications can be observed such as excessive familiarity, reduced attention to the entourage, unusual consumption of alcohol, compulsive shopping or even gambling (personal observations). Some are classically reported during severe depression and comprise patient isolation, withdrawal from work, anger, suicidal attempts or even violence [25,46,50]. Others such as episodes of excitement and exhaling can occur during typical episodes of hypomanic or manic episodes.

Imaging correlates of mood, cognitive or behavioral manifestations

The mood, cognitive or behavioral manifestations of CADASIL are not observed in the absence of cerebral lesions on MRI [1]. The detailed relationships between these different clinical manifestations and brain MRI lesions have not been fully investigated yet. However, accumulating evidence suggests that alterations in the functioning of specific cortico-subcortical networks are involved in most of these symptoms.

MRI white-matter changes are likely associated with mood alterations in CADASIL. They are always present when patients are diagnosed with depression [27,68]. In parallel, white-matter hyperintensities in sporadic cSVD are also associated with an increased risk of depression [69–71] both in elderly subjects [72] or in populations with psychiatric disorders [69,73]. Changes in white-matter connections related to the dorsolateral prefrontal and/or anterior cingulate cortex might be involved because of their role in mood regulation [72]. Modifications in the fronto-limbic white matter, tracts connecting the corpus callosum to the anterior cingulate cortex, the cingulate fibers within the para-hippocampal gyrus, the uncinate fasciculus or anterior thalamic radiations have been also related to mood disturbances [72,74]. The composition of the white matter itself, which is altered in CADASIL, is another potential source of mood changes. The loss of oligodendrocytes has been associated with mood modifications [75] and reduced white-matter compactness with emotional or mood control [76].

White matter damage is also likely related to the slower cognitive speed detected early in the course of CADASIL. Reduced cognitive speed can be detected in patients who present only with white matter hyperintensities in the absence of lacunes [77]. At this stage, impaired myelin may be involved in the reduced performance, particularly within myelinated axonal networks of frontal regions [78,79]. The location of lesions within the minor forceps or anterior thalamic radiations were found to be associated with cognitive slowing in CADASIL [80]. Accumulating lacunes are significantly associated with the severity of cognitive decline and incident lacunes have been related to the increasing cognitive slowdown during the course of the disease [81] as is reported in sporadic small vessel disease [82]. Impairment of executive function, memory and other cognitive skills progresses with further accumulation of lacunes in the white-matter and basal ganglia. Location of lesions in the cingulum bundle carrying anteroposterior connections may play a key role in the alteration of executive processes in CADASIL [83]. Recently, apathy was found to be related to a reduced fractional anisotropy within the right anterior cingulum, bilateral orbitofrontal-anterior cingulate white matter, right anterior limb of the internal capsule, body of the corpus callosum and left superior cerebellar peduncle (SCP), a neural network presumably involved in effort-based decision-making [67].

Accumulation of lacunes and development of cerebral atrophy are found to be related to the most severe clinical manifestations of the disease and to both cognitive and motor disability [18,84,85]. The number of lacunes at baseline or the occurrence of incident lacunes in longitudinal studies are associated with decrease in cognitive scores, increase of gait or balance difficulties, and worsening of disability [84, 86]. Lacunes occur after focal ischemic lesions and correspond to the most destructive focal tissue lesions that occur during the course of a small vessel disease. Not all focal ischemic lesions result in cavitation [87]. Lacunes predominate in the deepest regions of the brain, particularly in periventricular areas and/or within the gray nuclei. Accumulating evidence suggests also that lacunes at subcortical level have remote consequences at the cortical level [88]. They are also associated with secondary demyelination within both the white and gray matter as well along different fiber tracts and contribute to the development of cerebral atrophy and in particular of cortical atrophy [89,90]. Indeed, secondary cortical degeneration has been observed after the occurrence of incidental lacunes during the course of CADASIL and neuronal apoptosis was reported in the most connected layers within the cerebral cortex [88,91,92]. These findings may explain why cerebral atrophy is closely related to the severity of cognitive impairment in this disorder [88,93,94]. Morphological changes in the cortical sulci (depth or width) have been observed and correlated to executive performances or to the Mattis Dementia Rating scale in CADASIL patients [95]. Identical morphological changes in the mediofrontal and orbitofrontal cortex have been associated with apathy [96]. At the latest stage of the disease, diffuse atrophy is observed. Hippocampal shrinking may also result from secondary degenerative processes and major loss of underlying white-matter bundles [97]. It is independently associated with the severity of cognitive impairment [98]. Finally, the degree of cerebral atrophy may represent a synthetic marker reflecting the accumulation and severity of lesions at subcortical level which explains its high correlation in longitudinal studies with cognitive decline [99]. Notably, dilated perivascular spaces were also found to be independently associated with the severity of cognitive decline in a single study [100], but not microbleeds [101].

Treatment

We cannot recommend any specific treatment of proven efficacy to reduce mood, cognitive or behavioral disturbances during the course of CADASIL.

Different types of antidepressants are currently used for treating depression in CADASIL patients. Selective serotonine reuptake inhibitors are classically proposed, they are well tolerated and can improve symptoms in the vast majority of cases (personal observations). Increased dosage is sometimes needed in low or insufficient-response cases. Amitriptyline has been also used with some efficacy but should be avoided in the presence of cognitive impairment due to its anticholinergic effects [20]. In some cases, drug treatment was reported to be inefficient and electroconvulsive therapy has been occasionally used to treat persisting melancholic state [26,50]. Despite the lack of specific studies, the management of mood disorders obviously requires psychotherapeutic support. This should be adapted to each situation and each case and take into account the specific context of a familial disorder with devastating disease in often several close family members [102].

The only placebo-controlled randomized clinical trial was conducted with donepezil for improving cognitive impairment in symptomatic but nondemented patients. The results showed some improvement in various executive performances but did not provide any significant effect on global cognitive efficiency or daily activities [103]. Only in few cases, Galantamine, another cholinesterase inhibitor was found to provide some benefits in demented CADASIL patients [104]. Therefore, cholinesterase inhibitors cannot be recommended systematically in CADASIL patients.

Neuroleptics have been used transiently to reduce excitation, violent reactions or agitation .

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