

Neuropsychiatric manifestations in CADASIL

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited small-artery disease of mid-adulthood caused by mutations of the NOTCH3 gene. The disease is responsible for widespread white-matter lesions associated with lacunar infarctions in various subcortical areas. The disease is responsible for migraine with aura and ischemic strokes, and is associated with various degrees of cognitive impairment and with mood disturbances. CADASIL is considered as a unique model to investigate what is known as "subcortical ischemic vascular dementia." Recent data suggest that the number of lacunar infarctions and severity of cerebral atrophy are the main magnetic resonance imaging markers associated with cognitive and motor disabilities in this disorder. Mood disturbances are reported in 10% to 20% of patients, most often in association with cognitive alterations. Their exact origin remains unknown; the presence of ischemic lesions within the basal ganglia or the frontal white matter may promote the occurrence of these symptoms. Further studies are needed to better understand the relationships between cerebral lesions and both cognitive and psychiatric symptoms in this small-vessel disease of the brain.

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)¹ is an inherited small-artery disease of mid-adulthood caused by mutations of the *NOTCH3* gene on chromosome 19.² The exact frequency of CADASIL remains unknown. The disease has been diagnosed in European, Asian, African, and American, as well as in Australian families. In France, Germany, and the United Kingdom, several hundreds of CADASIL families have been identified.³⁻⁶ Based on a register for the disease in the West of Scotland, Ravzi et al estimated in 2004 that the prevalence of the *NOTCH3* gene mutation was about 4.14 per 100 000 adults in this population.⁷ This frequency is probably underestimated. CADASIL is still underdiagnosed, and may be one of the most frequent hereditary neurological disorders. It is considered as a model of "pure" vascular dementia related to small-vessel disease, and as an archetype of the so-called "subcortical ischemic vascular dementia." CADASIL is also responsible for mood disturbances, most often in association with cognitive impairment.

Pathophysiology

CADASIL is characterized by the presence of white-matter rarefaction and subcortical ischemic lesions of the brain, easily detected using magnetic resonance imaging (MRI). Macroscopic examination of the cerebral tissue

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shows a diffuse myelin pallor and rarefaction of the hemispheric white matter, sparing the U fibers.⁸ Lesions predominate in the periventricular areas and centrum semi-ovale. They are associated with lacunar infarcts located in the white matter and basal ganglia (lentiform nucleus, thalamus, caudate).^{9,10} The most severe hemispheric lesions are the most profound.^{8,11,12} In the brain stem, the lesions are more marked in the pons, and are similar to the pontine ischemic rarefaction of myelin described by Pullicino et al.¹³ Small, deep infarcts and dilated Virchow-Robin spaces are also associated with the white-matter lesions.

In CADASIL, the walls of cerebral and leptomeningeal arterioles are thickened with a significant reduction of the lumen⁸; thus, penetrating arteries in the cortex and white matter appear stenosed.^{14,15} Some inconstant features are similar to those reported in patients with hypertensive encephalopathy¹⁶: duplication and splitting of internal elastic lamina, adventitial hyalinosis and fibrosis, and hypertrophy of the media. However, a distinctive feature is the presence of a granular material within the media extending into the adventitia.^{8,11,17-21} The periodic acid Schiff (PAS) positive staining suggested the presence of glycoproteins; staining for amyloid substance and elastin is negative.^{9,11} Immunohistochemistry does not support the presence of immunoglobulins. In contrast, the endothelium of the vessels is usually spared. Sometimes, the smooth muscle cells are not detectable, and are replaced by collagen fibers.¹⁶ On electron microscopy, the smooth muscle cells appear swollen and often degenerated, some of them with multiple nuclei. There is a granular, electron-dense, osmiophilic material (GOM) within the media.²² This material consists of granules of about 10 to 15 nm in diameter. It is localized close to the cell membrane of the smooth muscle cells, where it appears very dense. The smooth muscle cells are separated by large amounts of this unidentified material.

CADASIL is caused by stereotyped mutations of the *NOTCH3* gene.² Unlike other members of the Notch gene family whose expression is ubiquitous, the *NOTCH3* gene is expressed only in vascular smooth muscle cells²³ of arterial vessels.²⁴ It encodes a single-pass transmembrane receptor of 2321 amino-acids, with an extracellular domain containing 34 epidermal growth factor-like (EGF) repeats (including 6 cystein residues) and 3 Lin-12 repeats associated with an intracellular and a transmembrane domains.^{2,25} This cell surface receptor mediates signal transduction with receptor ligands such

as Jagged (Jag) and Delta (D) on neighboring cells which are also type 1 transmembrane receptors.^{2,25-27} Domenga et al showed that *NOTCH3* is required specifically to generate functional arteries in mice by regulating arterial differentiation and maturation of vascular smooth muscle cells.²⁸ The stereotyped mis-sense mutations² or deletions²⁹ responsible for CADASIL are within epidermal-growth-factor-like (EGF-like) repeats and only located in the extracellular domain of the *NOTCH3* protein.³⁰⁻³² All mutations responsible for the disease lead to an uneven number of cystein residues.

The *NOTCH3* protein usually undergoes complex proteolytic cleavages, leading to an extracellular and a transmembrane fragment.³³ After cleavage, these two fragments form a heterodimer at the cell surface of smooth muscle cells. In CADASIL, the ectodomain of the *NOTCH3* receptor accumulates within the vessel wall of affected subjects.²³ This accumulation is found near but not within the characteristic granular osmiophilic material seen on electron microscopy. It is observed in all vascular smooth muscle cells, and in pericytes within all organs (brain, heart, muscle, lungs, skin). An abnormal clearance of the *NOTCH3* ectodomain from the smooth muscle cell surface is presumed to cause this accumulation.^{23,34,35} The exact mechanisms underlying this phenomenon have not yet been elucidated.

Vascular abnormalities observed in the brain are also detectable in other organs or territories.^{9,11} The granular and osmiophilic material surrounding the smooth muscle cells as seen with electron microscopy is also present in the media of arteries located in the spleen, liver, kidneys, muscle, and skin, and also in the wall of carotid and aortic arteries.^{9,11,36} Altered histochemical binding of plant lectins have been recently identified in the vessel walls of peripheral arteries.³⁷ These vascular lesions can be detected by nerve or muscle biopsy.^{38,39} The presence of the granular osmiophilic material in the skin vessels now allows confirmation of the *intra vitam* diagnosis of CADASIL using punch skin biopsies,^{11,40-43} although the sensitivity and specificity of this method have not yet been completely established. In some cases, the vessel changes may be focal, requiring a thorough evaluation of the biopsy specimen.⁴⁴ Joutel et al proposed using anti-*NOTCH3* antibodies to reveal the accumulation of *NOTCH3* products within the vessel wall in CADASIL patients as an alternative diagnostic method.⁴⁵

Transgenic mice expressing mutant *NOTCH3* develop the vascular alterations characteristic of CADASIL.⁴⁶

Experimental data show an impaired autoregulation of cerebral blood flow in these mice and suggest a decreased relaxation or increased resistance of cerebral vessels.⁴⁷ In addition, flow-induced dilation was significantly decreased and pressure-induced myogenic tone significantly increased in these arteries suggestive of impaired vascular mechanotransduction.⁴⁸

Neuropsychiatric manifestations

The natural history of CADASIL is summarized in *Figure 1*. The first clinical manifestations in CADASIL are attacks of migraine with aura, occurring between the ages of 20 and 40 years.^{4,41,49} They are observed in 20% to 30% of patients.

Ischemic manifestations, the most frequent clinical manifestations, are reported in 60% to 80% of patients, usually during the fourth and fifth decade.

Neuropsychiatric manifestations include mood disturbances and various degrees of cognitive impairment. They are observed at all stages of the disorder. A marked decline in cognitive performance is reported in most individuals after age 50 years. Dementia is usually detected at age >60 years, and is found nearly constantly at the end stage of the disorder.^{4,41,49} Psychiatric symptoms, mainly episodes of mood disturbances, are reported in 10% to 20% of patients during the course of the disease.^{4,5}

Cognitive impairment

Symptomatic patients can remain several years without any neuropsychological decline.⁵⁰ However, cognitive impairment and dementia represent the second commonest clinical manifestation in CADASIL, after acute ischemic symptoms.

The onset of cognitive deficit is usually mild and insidious, and its exact time is often difficult to ascertain. The cognitive changes may appear a long time before transient ischemic attacks (TIAs) or stroke.⁵¹ Cross-sectional studies⁵²⁻⁵⁵ have shown that early in the disease, cognitive functions, most frequently attention and executive functions, may be impaired. In a recent series of 42 patients, attention and executive functions were affected in nearly 90% of patients aged between 35 and 50.⁵⁵ These disturbances are often associated with alterations in attention and memory suggestive of dysfunction within the subcortical-frontal network.^{52,55,56} In contrast, other functions such as verbal episodic memory and visuospatial abilities

are usually preserved, and may remain spared until the late stages of the disease.

Some tests are particularly sensitive to the detection of the early cognitive changes. They include digit span backwards and forwards, the Trail Making Test part B, the Stroop test, and the Wisconsin Card Sorting test. The errors of CADASIL patients may predominantly affect the time measure in timed tasks (Stroop, Trail Making Test, symbol digit, digit cancellation) though errors in monitoring are also observed to a lesser extent.⁵⁴ Patients may also show poor strategy and planning when completing tasks such as the Wisconsin Card Sorting Test and the Rey-Osterreith memory test. Memory deficit may be associated with executive dysfunction, but its profile is usually distinct from dementias primarily involving the mesiotemporal temporal cortex such as Alzheimer's disease. This is illustrated by procedures such as those used in the Grober and Buschke test. This test allows differentiation of different phases of memory processes, and is likely to show the preservation of the encoding process even though the retrieval is impaired. It is composed of: (i) an encoding phase where 16 words belonging to 16 different semantic categories have to be retrieved; (ii) 3 phases of free recall and cued recall (the last being delayed); and (iii) a recognition test. In CADASIL, this test distinguishes a pattern characterized by low scores in immediate and delayed free recall, improving with cues and associated with relatively intact recognition. Intrusions may occur in the free recall task. This profile supports preservation of the encoding process, and anatomically, of the mesiotemporal cortex. It is still observed in about two thirds of CADASIL patients with dementia.⁵⁵

With aging, the cognitive decline becomes more homogeneous, with significant changes in all cognitive domains. This extension cannot be ascribed solely to the deterioration of executive performances, but appears to be related to additional alterations in instrumental activities,

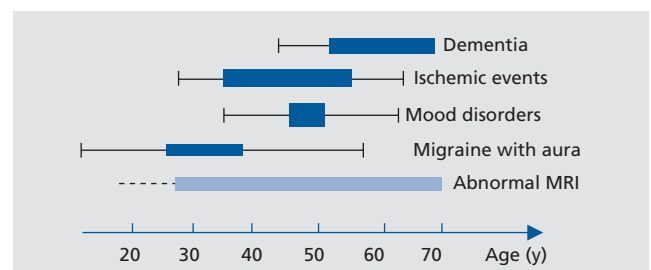


Figure 1. Natural history of CADASIL. MRI, magnetic resonance imaging

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language, and visuospatial abilities, and suggests a diffuse cortical dysfunction well beyond the subcortical-frontal circuits.⁵⁵ The development of cognitive impairment appears sometimes to be associated with the occurrence of stroke. Nevertheless, a cognitive deficit and even a dementia state may also occur in patients without any clinical history of stroke. The cognitive profile of CADASIL patients was analyzed before and after the occurrence of strokes in two cross-sectional studies, and showed some discrepant results. Amberla et al⁵³ reported that executive functions were more widely affected, with a significant mental slowing in CADASIL patients with a positive history of stroke. Conversely, Buffon et al observed that visuospatial abilities were mostly impaired in patients with stroke.⁵⁵ The cognitive deficit most often progresses in the total absence of ischemic events, mimicking in some cases a degenerative dementia.^{55,57,58} The temporal progression of cognitive symptoms varies among subjects from rapid and marked deterioration to stable or even slightly improving performances.⁵⁹

Dementia is reported in one third of symptomatic patients at the late phase of the disorder. The frequency of dementia increases considerably with age. Thus, about 60% of patients older than 60 years are demented,⁴ and more than 80% of deceased subjects were reported to be demented before death.⁵ When dementia is present, the neuropsychological deficit is usually extensive, involving not only executive functions, attention, and memory, but also reasoning and language performances.⁵⁵ Dementia is often associated with apathy. Conversely, severe aphasia, apraxia or agnosia are rare.^{55,56} In addition, demented individuals have a relative preservation of recognition and semantic memory.⁵⁵ Noteworthy, two thirds of them present improvement of memory with cues, which suggests that the encoding process is preserved even at the late stage of the disease, in contrast with the pattern of memory impairment in Alzheimer's disease. Dementia is observed in the absence of any other clinical manifestations in 10% of cases.⁵⁵ The frequency and severity of the cognitive decline are variable in different members of a given family. The variable location and severity of cerebral tissue damage may play a key role in this variability.^{60,61}

Dementia is always associated with pyramidal signs. Gait difficulties are present in 90%, urinary incontinence in 80% to 90%, and pseudobulbar palsy in half of demented individuals. At the end stage of the disorder, CADASIL patients become bedridden. In a large retrospective study

in 411 patients, Opherck et al found that the median age at onset for inability to walk without assistance was 59 years in men and 62 in women, and for bedriddenness, 62 years in men and 66.5 years in women.

Psychiatric symptoms

About one fifth of CADASIL patients experienced episodes of mood disturbances. Their frequency is widely variable between families.^{5,62} Episodes of major depression were reported by 10% of the 80 CADASIL patients investigated by Peters et al. In some cases, antidepressant drugs were found to be inefficient in relieving symptoms during the most severe episodes.

Few affected subjects have had severe depression of the melancholic type alternating with typical manic episodes suggesting bipolar mood disorder.⁶³ Based on this observation, the potential role of the *NOTCH3* gene was thus investigated in familial forms of bipolar disorder, but the results were negative.⁶⁴ The location of ischemic lesions in basal ganglia and the frontal location of white-matter lesions may play a key role in the occurrence of such mood disturbances in CADASIL patients.^{65,66}

In addition to the mood disorders, a variety of psychiatric manifestations can occur in CADASIL patients. Agoraphobia, addiction to alcohol, and psychotic symptoms have been already reported.^{4,5,67} The observation of schizophrenia in association with CADASIL appears anecdotal.⁶⁸

Most often, psychiatric manifestations are observed in patients after diagnosis and a history of ischemic symptoms with signal abnormalities at MRI examination. However these episodes can be inaugural, and may lead to misdiagnosis.^{5,62,69} Leyhe et al recently reported two cases admitted to a gerontopsychiatric hospital with psychopathological manifestations at the onset of the disorder.⁷⁰ The first case was a 66-year-old man who was described as a reserved, peaceful, and calm person and who became irritable, started to neglect himself and his duties, and presented a submanic episode which mildly improved after treatment with neuroleptic drugs. The patient started to consume alcohol again after years of abstinence. The second case was a 62-year-old woman with a 2-year episode of depressive symptoms who was initially successfully treated by amitriptyline. She was admitted to hospital because she deteriorated despite medication, developing paranoid ideas and melancholia. The psychopathological symptoms slowly improved on a

combination of antidepressant and anxiolytic drugs and neuroleptics. In both cases, the MRI examination and the family history were essential for diagnosis.

Correlations with cerebral tissue lesions

MRI is crucial for the diagnosis of CADASIL, and is much more sensitive than computerized tomography (CT)-scan. It is always abnormal in patients with neurological symptoms other than migraine attacks.^{1,5,41,71,72} MRI signal abnormalities can also be detected during a presymptomatic period of variable duration. They are observed as early as 20 years of age. After age 35, all subjects having the affected gene have an abnormal MRI.^{1,71} The frequency of asymptomatic subjects with abnormal MRI decreases progressively with aging, and becomes less than 5% after 60 years.⁷²

MRI shows, on T2-weighted images, widespread areas of increased signal in the white matter associated with focal hyperintensities in basal ganglia, thalamus, and brain stem (*Figure 2*).^{72,73} The extent of white-matter signal abnormalities is highly variable. It increases dramatically with age. In subjects under 40 years of age, T2 hypersignals are usually punctuate or nodular with a symmetrical distribution, and predominate in periventricular areas and within the centrum semi-ovale. Later in life, white-matter lesions are diffuse and can involve the whole of white matter, including the U fibers under the cortex.⁷²⁻⁷⁵ Scores of severity based on semiquantitative rating scales significantly increase with age, not only in the white matter but also in basal ganglia and brain stem. Frontal and occipital periventricular lesions are constant when MRI is abnormal. The frequency of signal abnormalities in the external capsule (two thirds of cases) and in the anterior part of the temporal lobes (60%) is noteworthy and particularly useful for differential diagnosis with other small-vessel diseases.⁷⁶⁻⁷⁸ T2 hyperintensities can be detected in the corpus callosum.^{75,79} Brain stem lesions predominate in the pons in areas irrigated by perforating arteries and can involve the mesencephalon.⁷⁴ In contrast, the medulla is usually spared.

On T1-weighted images, punctiform or larger focal hypointensities are frequent in the same areas and are detected in about two thirds of individuals with T2 hyperintensities⁷² (*Figure 2*). They are observed both in the white matter and the basal ganglia, but also in the brain stem and correspond mostly to lacunar infarctions. Numerous hypointensities on T1-weighted images may

also correspond to Virchow-Robin spaces which are more frequent and extensive in CADASIL than in healthy subjects. MRI signal abnormalities within the temporal white matter in CADASIL and particularly within the subcortical white matter, are considered as a characteristic feature of the disease. They are also caused by a distension of the perivascular space of perforating arteries at the level of the junction of gray and white matter, and by spongiosis in the surrounding parenchyma.⁸⁰ In contrast with the extent of white-matter hyperintensities weakly associated with the clinical severity,⁵⁴ the degree of white-matter microstructural damage measured with diffusion tensor imaging (DTI) appears strongly related to the clinical status in CADASIL.⁸¹ This is in agreement with the correlations observed between the clinical status and the load of T1 lesions within the white matter, which suggests that the degree of tissue destruction or neuronal loss is crucial for the appearance of disability in CADASIL.^{60,81,82}

The exact mechanisms of cognitive dysfunction in CADASIL remain unknown. The main hypothesis is that accumulation of subcortical lesions may damage in particular the striato-cortical circuits linking basal ganglia to frontal cortical areas, with possible secondary cortical degeneration.⁶⁰ This hypothesis is supported by evidence of strong correlations between cortical atrophy and the cognitive decline in the disease in both imaging and neuropathological studies. As described previously, severe cortical metabolic depression has indeed been observed by positron-emission tomography (PET) study in association with basal ganglia and thalamic infarcts in a

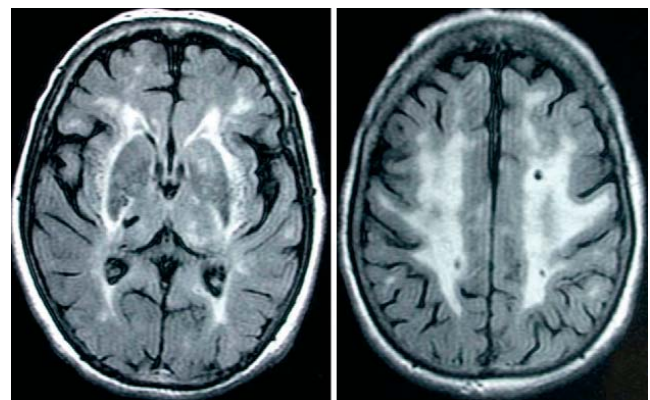


Figure 2. MRI of a 56-year-old woman with CADASIL suffering from depression and with executive dysfunction, and showing diffuse white-matter hyperintensities and small deep infarcts located in the thalamus and within the centrum semi-ovale.

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demented patient. The postmortem brain examination of a CADASIL case showed evidence of a diffuse loss of cortical neurons associated with cholinergic denervation.⁸³ In a recent neuropathological study, Viswanathan et al reported the presence of widespread neuronal apoptosis in the cerebral cortices of four CADASIL patients. Semiquantitative analysis suggested that the degree of cortical neuronal apoptosis was related to the extent of white matter lesions and to the intensity of axonal damage in subcortical areas⁸⁴ and was associated with the severity of cognitive impairment. Therefore, subcortical axonal damage may induce cortical apoptosis through deafferentation and/or retrograde neuronal degeneration in CADASIL.

Disruption of cortical connections may affect striatocortical circuits relaying to the thalamus and basal ganglia as well as cortical networks. This is supported by recent DTI findings from Sullivan et al, who observed: (i) a strong correlation between mean diffusivity measured in the thalamus (which could reflect either direct pathological damage or secondary degeneration due to disruption of white matter tracts relaying in this structure) and executive dysfunction⁸⁵; (ii) executive performances also correlated with mean diffusivity in the anteroposterior fasciculus of the cingulum bundle which connects the dorsolateral prefrontal lobe with more posterior cortical regions including the hippocampal formation.⁸⁶

Other clinical manifestations

In contrast with migraine without aura, whose frequency is identical to that estimated in the general population, migraine with aura is reported in 20% to 40% of CADASIL patients, a frequency 4- to 5-fold higher than in the general population. Among pedigrees, this frequency appears extremely variable. The mean age at onset is between 28 to 30 years,^{49,87} with a wide range from 6 to 48 years. In the largest series, that of Vahedi et al, the frequency of attacks appears extremely variable among affected individuals, from two per week to one to every 3 to 4 years.⁸⁷ Triggering factors of migraine with aura are similar to those of migraine in the general population (stress, flashing lights, fatigue, physical exercise, head trauma, strong smells, etc).⁸⁷ The most frequent symptoms are visual, sensory, or aphasic. Motor symptoms are reported in one fifth of CADASIL patients who have attacks of migraine with aura. In contrast with the aura symptoms reported in the general population, more than

half of patients have a history of atypical aura such as basilar, hemiplegic, or prolonged aura (International Headache Society criteria⁸⁸). A few patients even suffer from severe attacks with unusual symptoms such as confusion, fever, meningitis or coma,⁸⁹⁻⁹¹ exceptionally reported in migraine with aura.^{92,93}

Ischemic manifestations are the most frequent clinical events in CADASIL: 60% to 85% of patients have had TIAs or completed strokes.^{4,6,94} They occur at a mean age of 45 to 50 years (extreme limits from 20 to 70 years).^{4,5,20,41} Age of onset does not differ between men and women. In a recent follow-up study, Peters et al estimated the incidence rate of stroke at 10.4 per 100 person-years.⁵⁹ Two thirds of them are classical lacunar syndromes: pure motor stroke, ataxic hemiparesis, pure sensory stroke, sensory-motor stroke.⁵ Other focal neurologic deficits of abrupt onset are less frequent: dysarthria, either isolated or associated with motor or sensory deficit, monoparesis, paresthesiae of one limb, isolated ataxia, nonfluent dysphasia, hemianopia.⁵

Five percent to 10% of CADASIL patients experience seizures, either focal or generalized.^{4,20,95} They are usually reported in patients with a positive history of stroke. Epilepsy is usually well-controlled by current antiepileptic drugs.

Other neurological manifestations have occasionally been reported in CADASIL. Parkinsonism has been diagnosed in a few patients whose clinical presentation can mimic, in rare cases, progressive supranuclear palsy.⁹⁶ Deafness of acute or rapid onset has been reported in a few subjects, but its exact frequency remains unknown.⁷¹ Rufa et al reported an acute unilateral visual loss secondary to a nonarteritic ischemic optic neuropathy in a single 60-year-old case who was demented, but this had occurred 33 years earlier at age 27.⁹⁷

The lack of cranial nerve palsy, spinal cord disease, and symptoms of muscular origin is noteworthy in CADASIL. The exact cause of the radiculopathy reported in one case by Ragno et al remains undetermined.⁹⁸ Recently, several cases belonging to Italian and Chinese families with clinical and electrophysiological signs of peripheral sensorimotor neuropathy were described.^{99,100}

Conclusion

Neuropsychiatric manifestations are common in CADASIL, a genetic small-vessel disease leading to “subcortical ischemic vascular dementia.”

Cognitive alterations are frequent, and can be detected at the early stages of the disorder, as early as the third decade. They can remain insidious for several years, mainly involving executive functions and attention. A decline in cognitive performances is usually observed after the fifth decade, in association with the recurrence of ischemic manifestations, which leads progressively to dementia associated with pseudobulbar palsy, gait disturbances, and motor impairment.

Psychiatric episodes may also occur during the course of the disorder, rarely before 40 years, most frequently after the occurrence of ischemic events during the fifth or sixth decade. Episodes of mood disorders, the most frequent psychiatric symptoms, are rarely isolated and are often

associated with executive dysfunction. When they are inaugural, different features such as their resistance to antidepressant drugs, the association with neurological signs (pyramidal symptoms, cognitive alterations), and the detection of white-matter MRI abnormalities, as well as a positive family history of stroke and dementia, are helpful for raising the diagnosis of CADASIL.

CADASIL is a unique model to investigate the relationships between subcortical ischemic lesions and the cognitive and psychiatric status in small vessel diseases. Further studies are needed to better understand the exact impact of cerebral tissue lesions, and the role of their distribution or of their severity on the occurrence of cognitive and psychiatric symptoms in this disorder. □

Manifestaciones psiquiátricas en CADASIL

CADASIL (arteriopatía cerebral autonómica dominante con infartos subcorticales y leucoencefalopatía) es una enfermedad heredada, que afecta pequeñas arterias durante la adultez media y es causada por mutaciones del gen Notch3. La enfermedad es la responsable de extensas lesiones de la sustancia blanca asociadas con infartos lacunares en varias áreas subcorticales. La enfermedad es responsable de migraña con aura y accidentes vasculares isquémicos, y se asocia con deterioro cognitivo de grado variable y con trastornos del ánimo. CADASIL se considera un modelo único para estudiar lo que se conoce como "demencia vascular isquémica subcortical". Datos recientes sugieren que el número de infartos lacunares y la gravedad de la atrofia cerebral son los principales marcadores en las imágenes de resonancia nuclear magnética que se asocian con las incapacidades cognitivas y motoras en esta enfermedad. Los trastornos del ánimo ocurren en el 10% a 20% de los pacientes, y con gran frecuencia se asocian con alteraciones cognitivas. Aun no se conoce el origen exacto de estos síntomas, pero la presencia de lesiones isquémicas en los ganglios basales o en la sustancia blanca frontal puede facilitar la aparición de estos. Se requiere de futuros estudios para una mejor comprensión de la relación entre las lesiones cerebrales y los síntomas cognitivos y psiquiátricos en esta enfermedad cerebral de pequeños vasos.

Manifestations neuropsychiatriques du CADASIL

Le CADASIL, ou Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy est une affection héréditaire des petites artères cérébrales survenant chez l'adulte d'âge moyen, due à des mutations du gène Notch3. La maladie est responsable de lésions diffuses de la substance blanche associées à des infarctus lacunaires au niveau des régions sous-corticales cérébrales. Elle est à l'origine de crises de migraine avec aura, d'accidents ischémiques cérébraux et est associée à différents degrés d'altération cognitive et à des troubles de l'humeur. CADASIL est considéré comme un modèle unique d'étude des "démences sous-corticales d'origine ischémique". Des données récentes suggèrent que le nombre d'infarctus lacunaires et la sévérité de l'atrophie cérébrale sont les principaux marqueurs de la maladie associés au handicap cognitif et moteur de la maladie. Les troubles de l'humeur sont rapportés par 10 à 20 % des patients, le plus souvent en association avec des altérations cognitives. Leur origine exacte demeure indéterminée, la présence de lésions ischémiques au niveau des noyaux gris ou au sein de la substance blanche frontale pourrait favoriser l'apparition de ces symptômes. Des études complémentaires sont nécessaires pour mieux comprendre les relations entre les lésions cérébrales et les symptômes cognitifs et psychiatriques observés au cours de cette maladie des petits vaisseaux du cerveau.

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