Research, Society and Development, v. 11, n. 5, e21311528005, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i5.28005

Clinical manifestations, laboratorial findings and mechanisms of CADASIL: An integrative review

Manifestações Clínicas, achados laboratoriais e mecanismos do CADASIL: Uma revisão integrativa

Manifestaciones clínicas, hallazgos de laboratorio y mecanismos de CADASIL: Una revisión integradora

Received: 03/12/2022 | Reviewed: 03/20/2022 | Accept: 03/28/2022 | Published: 04/04/2022

Matheus dos Santos do Nascimento Carvalho
ORCID: https://orcid.org/0000-0003-4907-1750
Universidade Estadual de Ciências da Saúde de Alagoas, Brasil
E-mail: matheus2029mpc@gmail.com
Jordana Alexandre de Oliveira Santos
ORCID: https://orcid.org/0000-0001-7472-5942
Universidade Estadual de Ciências da Saúde de Alagoas, Brasil
E-mail: jordana.santos@academico.uncisal.edu.br
Mellissa da Rocha Carvalho
ORCID: https://orcid.org/0000-0002-4699-1343
Universidade Estadual de Ciências da Saúde de Alagoas, Brasil
E-mail: mellissa.carvalho@academico.uncisal.edu.br
Nathália Dantas Barbosa
ORCID: https://orcid.org/0000-0003-3502-7468
Universidade Estadual de Ciências da Saúde de Alagoas, Brasil
E-mail: nathalia.barbosa@academico.uncisal.edu.br
Lucas Costa de Melo
ORCID: https://orcid.org/0000-0002-4332-6356
Universidade Estadual de Ciências da Saúde de Alagoas, Brasil
E-mail: lucas.costa.melo@academico.uncisal.edu.br
Fernanda Helen Melo da Costa
ORCID: https://orcid.org/0000-0002-7887-0386
Universidade Estadual de Ciências da Saúde de Alagoas, Brasil
E-mail: fernanda.costa@academico.edu.br
João Pedro Fernandes de Carvalho
ORCID: https://orcid.org/0000-0003-0325-712X
Universidade Estadual de Ciências da Saúde de Alagoas, Brasil
E-mail: joao.pedro@academico.uncisal.edu.br
Euclides Maurício Trindade Filho
ORCID: https://orcid.org/0000-0001-6819-1673
Universidade Estadual de Ciências da Saúde de Alagoas, Brasil
E-mail: euclides.trindade@uncisal.edu.br

Abstract
This integrative literature review study aimed to analyze the clinical and laboratory findings, in addition to the treatment of case reports of CADASIL from the last 5 years. The database used in the search was PubMed, with the following descriptors: “CADASIL”, “case report”, in addition to the use of the Boolean operator (AND). The final sample was 25 baseline studies. Although CADASIL is caused by a genetic mutation, there was a case in which COVID-19 infection was the beginner of the manifestations of a patient with a previous mutation. In the exams, most have shown damages in MRI, with confluent hypertensive foci, microinfarcts, stenosis and even brain atrophy. Cases were also recorded in which the disease presented parkinsonian syndrome, symptoms of atypical paraplegia, mood alterations and transient ischemic attack. In the study it was perceptive the manifestations in families with this genetic disease. The symptons can be manifested in hetero or homozygous, and may cause mental disorders, headache and stroke. The clinical variety shows its complexity, requiring studies to understand all its pathophysiology.There is no cure for this disease, so its treatments were mainly to control the symptoms.
Keywords: CADASIL; NOTCH3; MRI; Cerebral infarct.

Resumo
Este estudo de revisão integrativa da literatura teve como objetivo analisar os achados clínicos e laboratoriais, além do tratamento de relatos de casos de CADASIL dos últimos 5 anos. A base de dados utilizada foi o PubMed, com os seguintes descritores: “CADASIL”, “case report”, além do uso do operador booleano (AND). A amostra final foi de 25 estudos de linha de base. Embora o CADASIL seja causado por uma mutação genética, houve um caso em que a infecção por COVID-19 foi o responsável pelo início das manifestações de um paciente com mutação prévia. Nos exames, a maioria mostrou danos na

RM, com focos hipertensivos confluentes, microinfartos, estenoses e até atrofia cerebral. Também foram registrados casos em que a doença apresentava síndrome parkinsoniana, sintomas de paraplegia atípica, alterações de humor e ataque isquêmico transitório. No estudo foi perceptível as manifestações nas famílias com esta doença genética. Os sintomas podem se manifestar em hetero ou homozigose, podendo causar transtornos mentais, cefaléia e acidente vascular cerebral. A variedade clínica mostra sua complexidade, necessitando de estudos para entender toda a sua fisiopatologia. Não há cura para esta doença, por isso seus tratamentos foram principalmente para controlar os sintomas.
Palavras-chave: CADASIL; NOTCH3; MRI; Infarto cerebral.

Resumen
Este estudio integrador de revisión de la literatura tuvo como objetivo analizar los hallazgos clínicos y de laboratorio, además del tratamiento de los informes de casos de CADASIL de los últimos 5 años. La base de datos utilizada fue PubMed, con los siguientes descriptores: "CADASIL", "case report", además del uso del operador booleano (AND). La muestra final consistió en 25 estudios de referencia. Aunque CADASIL está causado por una mutación genética, hubo un caso en el que la infección por COVID-19 fue la responsable de la aparición de manifestaciones en un paciente con una mutación previa. En la exploración, la mayoría mostraba daño en la resonancia magnética, con focos hipertensivos confluentes, microinfartos, estenosis e incluso atrofia cerebral. También se registraron casos en los que la enfermedad presentó síndrome parkinsoniano, síntomas de paraplejía atípica, cambios de humor y accidente isquémico transitorio. En el estudio se notaron las manifestaciones en familias con esta enfermedad genética. Los síntomas pueden manifestarse en hetero u homocigosidad, y pueden causar trastornos mentales, dolor de cabeza y accidentes cerebrovasculares. La variedad clínica muestra su complejidad, requiriendo estudios para comprender toda su fisiopatología. No existe cura para esta enfermedad, por eso que sus tratamientos fueron principalmente para controlar los síntomas.
Palabras clave: CADASIL; NOTCH3; MRI; Infarto cerebral.

1. Introduction

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a genetic disease of monogenic etiology, responsible for a wide variety of manifestations among patients. The alteration responsible for this disease is found in the NOTCH 3 gene mutation, present in the short arm of chromosome 19, whose mutations were reported in exons 2 to 24 (Ferrante et al., 2020; Correia, 2011).

The mutations are usually detected in exons 3 and 4 with a dominant allele pattern, so it manifests in both homozygous and heterozygous states. Thus, the proband who has such a disease usually has cases of family history, although there may be an unprecedented mutation in the proband, also called missense (Sari et al., 2019).

NOTCH3 gene is responsible for the formation of the homonymous protein present in a transmembrane way in cells of the muscular wall of the vessels, with the function of vascular stability. When some alteration occurs in such gene, it tends to cause damage to the vessel walls, which will be manifested by vascular changes and certain histological findings, such as the accumulation of proteins deposits known as granular osmiophilic material (GOM) near the walls of vascular smooth muscle. Such osmiophilic material has a non-homogeneous electron density and can be surrounded by electron-lucent halo (Lorenzi et al., 2017; NORD, 2021).

These histological changes are responsible for the various manifestations, which include vascular changes, such as vasculitis or even more serious manifestations, such as ischemic stroke. It is worth mentioning that most of these vascular lesions occur in nervous tissues, which will lead to lacunar infarctions in the brain and spinal cord, causing neurological disorders, paresis, hypoesthesia, headaches or even psychiatric manifestations, such as dementia, memory or speech impairment (André, 2010).

This disease has no predisposition for sex and has an occurrence of 2 to 5 people in every 100,000 people, and his diagnosis is based mainly on suspicion of migraine, cortical infarctions with cases in the family and typical findings on MRI. Also, based on its manifestations, CADASIL can be categorized into stages, which summarize that the more the years go by, the worsening of its symptoms occurs, however the speed of this degeneration may vary, and some patients may remain asymptomatic. In view of this, this work aims to expose and analyze the findings on the clinical manifestations recorded in the literature on the CADASIL disease, as well as to expose the possible mechanisms of action of this disease that explain the findings described (Correia, 2011).

2. Methodology

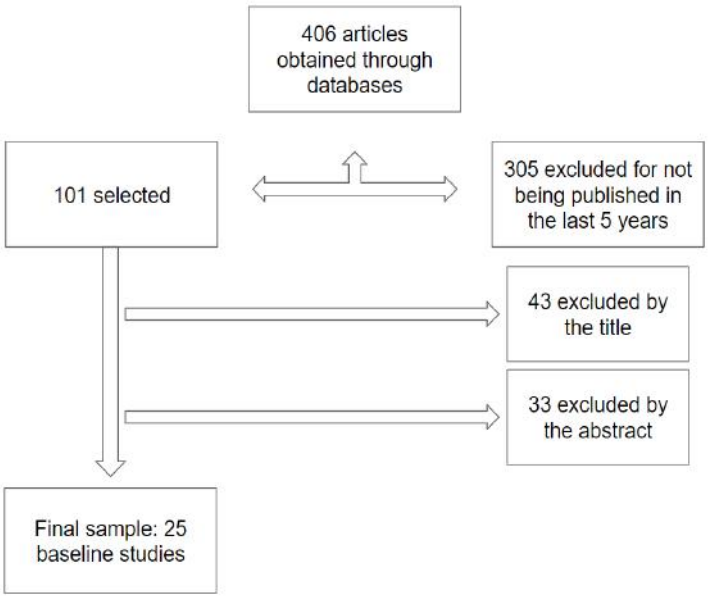
This study was carried out in December 2021, through an integrative review, used within the scope of Evidence-Based

Practice, in which previous studies are analyzed, in order to synthesize knowledge and assist in conduct and decisions. This review method is consisting of six steps: 1) identification of the theme and guiding question; 2) establishment of inclusion and exclusion criteria; 3) data collection from selected articles; 4) critical analysis of the articles in order to classify the evidence found; 5) interpretation of results; 6) synthesis of knowledge.

The database used in the search was PubMed, with the following descriptors: "CADASIL", "case report", in addition to the use of the Boolean operator (AND). Only full-text articles in English, Spanish and Portuguese that referred to the topic and were case reports described in the last 5 years were included in the sample. Other research modalities and those whose theme did not correspond to the proposal of the present study were excluded.

Initially, using the descriptors in PubMed, 406 references were identified. By selecting only articles from the last 5 years, the sample was reduced to 101 publications. After reading the titles and abstracts, 76 articles were excluded because they were not case reports or because they did not deal with the topic. Finally, 25 articles (Figure 1) were read in full and made up the sample of the integrative literature review.

Figure 1 - Flow diagram for selecting articles for integrative review.



Source: Authors (2022).

3. Results and Discussion

The search returned 56 articles. After reading the titles, 30 were excluded because they were not the subject of the review. After reading the abstracts, 25 articles on the researched topic were selected. Based on the literature review carried out, it was possible to detect the different clinical presentations promoted by CADASIL The main findings are shown in Table 1.

Table 1 - Studies published between 2017 and 2021 in the researched database that were selected for the integrative review.

Author	Age/Sex	Country	Cause	Family Cases	Exams results	Psychiatric manifestations	Neurological Manifestations	Vascular Manifestations	Treatment
Joshi *et al.* (2017)[7]	23 years old/female	Australia	NOTCH3 gene mutation in exon 3	Mother had the same mutation and headache	MRI findings	Not mentioned	Migraine	Not mentioned	Not mentioned
Joshi *et al.* (2017)[7]	56 years old/male	Australia	NOTCH3 gene mutation	Not mentioned	MRI findings	Decreased mood, anxiety and forgetfulness	Migraine and paresthesia	Not mentioned	Not mentioned
Chen *et al.* (2018)[8]	51 years old/female/	New Zealand	NOTCH3 gene mutation	Children had epilepsy and CADASIL	MRI findings	Cognitive deficit	Focal and generalized epilepsy and migraine	Not mentioned	Not mentioned
Mishra *et al.* (2018)[9]	32 years old/male	India	NOTCH3 gene mutation	Not mentioned	MRI and skin biopsy findings	Cognitive changes	Ataxic gait	Not mentioned	2nd generation antipsychotics
Paraskevas *et al.* (2018)[10]	38 years old/female	Greece	Heterozygous genetic mutation NOTCH3 of exon 4	16-year-old son with headache, father and grandmother suffered from headache and died of stroke	MRI findings	Anxious and depressed	Headache and vertigo	Not mentioned	Not mentioned
Paraskevas *et al* (2018).[10]	37 years old/female	Greece	Heterozygous genetic mutation NOTCH3 of exon 4	Not mentioned	MRI findings	Depression	Headache	Not mentioned	Paracetamol and sertraline
Sakiyama *et al.* (2018)[11]	67 years old/male	Japan	NOTCH3 heterozygous missense mutation in exon 3	Not mentioned	MRI findings, elevated PR3-ANCA	Not mentioned	Reduced reflexes and muscle weakness	Not mentioned	Not mentioned
Schiess *et al.* (2018)[12]	28 years old/female	USA	NOTCH3 heterozygous genetic mutation in exon 22	Mother with the same mutation and migraine	MRI findings and altered CSF	Cognitive damage and aggression	Urinary incontinence and tandem gait	Not mentioned	Not mentioned
Sweeney (2018)[13]	47 years old/male	Ireland	NOTCH3 heterozygous genetic mutation	Father had multiple sclerosis	MRI findings	Not mentioned	dysarthria	vasculitis	Not mentioned
Ebihara *et al.* (2018)[14]	50 years old/male	Japan	Heterozygous genetic mutation NOTCH3 of	Family history (stroke and depression)	MRI findings	Depression	Stroke	Hypertension	Not mentioned

			exon 24						
Anamnart *et al.* (2019)[15]	50 years old/male	Thailand	NOTCH3 homozygous genetic mutation	Sister (cognitive decline and slowness)	CT findings of the brain	Organic mood disorder	Convulsions, hemiparesis and slowness of movement	Ischemic stroke	Aspirin and phenytoin
Dunphy, *et al*. (2019)[16]	35 years old/male	United Kingdom	NOTCH3 heterozygous missense mutation in exon 3	Not mentioned	Findings on CT, ECG, echocardiograph yand MRI	Dysphasia	Mental confusion	Ventricular hypertension and hypertrophy and atheromatous plaques	Amlodipine, losartan, atorvastatin and aspirin
Jing *et al.* (2019)[17]	35 years old/male	China	NOTCH3 genetic mutation in exon 3	Mother had stroke and dementia	MRI findings	Not mentioned	Migraine and muscle weakness	Transient ischemic attack	Not mentioned
Saleem *et al*. (2019)[18]	28 years old/female	USA	missense NOTCH3 mutation in exon 11	Mom had multiple sclerosis	MRI findings	Mood alterations	Blurred vision	Not mentioned	Methylprednisolone, aspirin and statin
Sari *et al.* (2019)[3]	41 years old/female	Turkey	NOTCH3 genetic mutation	Same genetic alteration in niece, sister and father. Mother died of cerebrovascular disease	MRI findings, EEG change	Altered judgment, visual and auditory hallucination	Dizziness,diplopia, cerebellar ataxia and seizure	Not mentioned	Sodium valproate, lamotrigine, risperidone, donepezil and memantine
Sari *et al.* (2019)[3]	37 years old/female	Turkey	NOTCH3 genetic mutation	Sister with monthly tension headache	High C-reactive protein, ANA positive	Moderate depression	Headache and dizziness	Not mentioned	Clopidogrel and venlafaxine
Tsanaxidis *et al.* (2019)[19]	61 years old/female	United Kingdom	NOTCH3 genetic mutation	Not mentioned	ECG findings, changes in echocardiography and angiography	Not mentioned	Not mentioned	Myocardial infarction, SCAD and angina	Glycerin trinitrate,antiplatelet agents and aspirin
Zhang *et al*. (2019)[20]	32 years old/male	China	NOTCH3 genetic mutation	Not mentioned	MRI findings and sural nerve biopsy findings	Not mentioned	Facial paralysis and limb weakness	Middle cerebral artery atherosclerotic stenosis	Aspirin and atorvastatin
Ganesan *et al*. (2020)[21]	42 years old/male	Ireland	NOTCH 3 heterozygous genetic mutation in	Not mentioned	MRI and skin biopsy findings	Memory and language affected and dementia	Reduction of limb dexterity	Not mentioned	Not mentioned

			exon 6						
He *et al.* (2020)[22]	60 years old/male	China	NOTCH3 homozygous gene mutation in exon 11	Brother and son had the same mutation. Father had ischemic stroke	Findings on MRI and USG with Doppler	Moderate cognitive impairment	Ataxia, muscle weakness	Hypertension, ischemic stroke, interventricular septal hypertrophy and cerebral arteriosclerosis	Not mentioned
He *et al.* (2020) [22]	59 years old/male	China	NOTCH3 homozygous genetic mutation	Not mentioned	MRI findings	Language and mild cognitive impairment	Gait ataxia and dysarthria	Transient ischemic attack	Not mentioned
Jouvent *et al.* (2020)[23]	50 years old/female	French	NOTCH3 genetic mutation	Not mentioned	MRI findings	Severe bipolar disorder and depressive episodes	Not mentioned	Not mentioned	Fluoxetine and valpromide
Motolese *et al.* (2020)[24]	48 years old/male	Italy	Heterozygous genetic mutation exon 6 NOTCH3	Stroke cases (grandfather, maternal uncles), depression (mother)and neurological deficit (sister)	Findings on MRI and CT	Not mentioned	Hemiplegia, facial palsy, paraparesis	Acute ischemic stroke	Antiplatelet therapy and methylprednisolone
Park *et al.* (2020)[25]	50 years old/female	South Korea	Heterozygous genetic mutation NOTCH3 of exon 25	Not mentioned	Skin biopsy findings and MRI findings	Memory affected, mild depression and mild cognitive impairment	Dysarthria, dysdiadochokinesia and unsteady gait	Mild dyslipidemia	Aspirin and phenytoin
Uppal *et al.* (2020)[26]	64 years old/female	USA	NOTCH3 gene mutation of exon 19	Not mentioned	MRI findings	Verbal heteroaggression, emotional lability, mania and psychosis	Not mentioned	Not mentioned	Bupropion, amphetamine/dextroamphetamine, quetiapine and lithium carbonate
Ameer *et al.* (2021)[27]	40 years old/male	Pakistan	Missense genetic mutation NOTCH3 of exon 19	Not mentioned	MRI findings, positive anti-MOG	Not mentioned	Headache, vomiting, photophobia and seizure	Not mentioned	Lorazepam, dihydroergotamine (DHE), nitroglycerin, corticosteroid, donepezil, furosemide and captopril.

Spagnolo *et al.* (2021)[28]	60 years old/male	Italy	Exon 6 NOTCH3 gene mutation	Daughter has epileptic seizures and mother died of heart attack	MRi findings	Impairment of memory and attention	Gait disturbance and resting tremor	Not mentioned	L-dopa
Lahkim *et al.* (2021)[29]	51 years old/male	Morocco	NOTCH3 genetic mutation	Similar cases in relatives	MRI findings	Not mentioned	Migraines	Not mentioned	Antiplatelet agent and analgesics
Rajendran *et al.* (2021)[30]	45 years old/female	United Kingdom	Gene mutationNOTCH3e COVID-19	Father had stroke	Brain CT findings, MRI findings	Acute confusion	Dysarthria	Vasculitis	Not mentioned

Source: Authors (2022).

Firstly, CADASIL is known to be a genetic disease caused by missense alterations in the NOTCH 3 gene. However, in the present study, there was a case report of a patient who had no cases of CADASIL in the family and who developed the classic symptoms of white matter hyperintensity and lacunar infarctions in the exams after a SARS-CoV-2 infection, although it was later shown that he had a NOTCH3 gene mutation. This shows the theory that the virus may act as a trigger for the onset of symptoms. Besides that, the virus with his property to generate hypercoagulable state, direct neuroinvasion and high immune response may contribute to the findings of cortical microinfarcts, with occlusion of vessels (Sari et al., 2019; Dunphy et al., 2019; Rajendran et al., 2021).

CADASIL disease is usually progressive and its clinical manifestations occur around the third and fourth decade of life. Nevertheless, based on the data provided in the tables, it is noticeable that the reported cases ranged from people aged 23 years old, ranging up to the age of 67 years. The absence of children raises the hypothesis that either a good part of the clinical manifestations appear years later, or they intensify to a point of leading the patient to seek a medical center after some decades. Although in a report by Paraskevas et al. (2018), the 16 year old son of the proband was already complaining of headaches, but there was still no reference to whether he also has CADASIL, and in the study by Mishra et al. (2018) reveals that the patient has had symptoms since the age of 14, which have progressively worsened (Ferrante et al., 2020).

It is also worth mentioning that some family members may not have had CADASIL, but may have symptoms of the spectrum of manifestation of this disease, as in the study by Sari et al. (2019), in which the proband's mother died of cerebrovascular disease and had a history of epilepsy, while her father had cerebrovascular disease and senile dementia, as well as the study by Motolese et al. (2020), in which the proband had a grandfather, 2 cousins, and 2 maternal uncles who had a stroke, his mother had depression, and his sister had focal neurological deficits and hemiparesis. Such information suggests a family history of neuroinflammation, which ends up manifesting itself in different ways in each person.

NOTCH 3 gene mutations, in addition to the exons, which may vary in each case, also vary in their alleles, and can be found in heterozygous or homozygous forms. In the present study, 10 heterozygous and only 3 homozygous cases were related. So, such changes may explain the various symptoms reported in the family. In the study of Sari et al. (2019), the proband was homozygous for the mutation and had a niece who was also homozygous, but her sister and father were heterozygous, who had different clinical manifestations. Thus, the different phenotypes among patients suggest that this disease is influenced, in addition to genetic factors, by external factors. Furthermore, there is no record of whether the homozygous mutation is responsible for more severe clinical manifestations. About the exons, most showed alterations in exon 3, with a rare form described by Park et al. (2020) mutation in exon 25. Furthermore, it is interesting that cases prevailed in Asian countries, especially China, although they have been reported from all continents (He et al., 2020).

Initially, a lot of exams are made to carry out the differential diagnosis. Due to the variety of signs and symptoms of CADASIL, it is usually confused with other diseases, such as multiple sclerosis (MS), central nervous system (CNS) infections, transient ischemic attack (TIA), acute disseminated encephalomyelopathy (ADEM) and other hereditary diseases. However, after the negativity of these tests, CADASIL is diagnosed by genetic study (Ameer et al., 2021).

The classic manifestations of magnetic resonance are white matter hyperintensity (WMH), together with the finding of lacunar infarctions. One of the cases, Mishra et al. (2018) demonstrated confluent and discrete hyperintense focus on T2 in regions such as deep white matter and subcortical of the cerebral hemispheres, bilateral basal ganglia, brainstem and thalamus. While in a study by Motolese et al. (2020), these multiple hyperintensities were also present in the cerebellum and spinal cord, both in the anterior and posterior column. Another type of lesion frequently found were diffuse white matter lesions, involving the bilateral periventricular white matter, the semioval center region and the anterior temporal lobes (He et al., 2020).

Moreover, there were also findings of cerebrovascular lesions, such as MRI of the head, which demonstrated enlarged perivascular spaces with small lacunar infarcts, and evident microhemorrhages. And cases of acute cerebral infarctions and white matter hyperintensity, followed by right middle cerebral artery stenosis with intraplaque hemorrhage. Rare finding have shown a MRI with global atrophy, confluent white matter lesion, ring lesion in the right middle cerebellar peduncle and lesion in the right corona radiata (Schiesse et al., 2018; Dunphy et al., 2019; Zhang & Zhang, 2019).

Interesting study reported by Jouvent et al. (2020), a follow-up was performed for 15 years of MRI in the patient's FLAIR and they recorded an increase in ventricles and a global reduction of the entire brain volume, in a way that the rates of reduction varied periodically, reaching a reduction of 6.7% of its volume between 2010 and 2012, but there was a growth of 4.5% between 2014 and 2015.

There have been cases of classic leukoencephalopathies, in which MRI of the brain revealed a marked leukoencephalopathy in the frontal lobes with seven ischemic lacunar lesions. And in a more atypical case, the patient had severe leukoencephalopathy, with involvement of the lobes, right parietal cortical/subcortical gliotic area, suggestive of a previous ischemic stroke, several lacunar infarcts and cerebral microbleeds were identified in the basal ganglia and in the left temporal lobe. This was clinically manifested by strength deficits, sensory symptoms, dysarthria, horizontal ophthalmoplegia, left central facial palsy and paraparesis that impaired autonomous gait (Motolese et al., 2020; Lahkim et al., 2021).

In other tests besides neuroimaging, serological analysis revealed increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). In another case report, anti-myelin oligodendrocyte glycoprotein (anti-MOG) was tested and was positive, followed by an MRI that showed FLAIR diffusions in the parietal, periventricular and occipital regions, which was manifested by headache with photophobia, seizures and progressive weakness in the right arm (Sari et al., 2019; Ameer et al., 2021).

Another test widely used in CADASIL diagnosis was skin biopsy. These tend to reveal the frequent granular osmiophilic deposits in the basal lamina of a small blood vessel with degeneration and loss of smooth muscle cells under the electron microscope, which is a characteristic finding of the disease (Mishra et al., 2018).

Faced with such changes in the exams, the various clinical manifestations arise. It is observed that there is no pattern in these manifestations, in a way that psychiatric, neurological or vascular aspects can be reported and all of them vary between patients. Regarding psychiatric manifestations, findings such as decline in academic performance, self-care, anxiety, depression, impaired judgment, episodes of memory and speech impairment, paranoid ideas and depression have predominated. Some have been diagnosed with disorders such as organic mood disorder, adjustment disorder, severe bipolar disorder, and mania with psychosis (Joshi et al., 2017; Mishra et al., 2018; Anamnart et al., 2019; Jouvent et al., 2020; Uppal et al., 2020).

All these psychiatric manifestations were usually analyzed by mental examinations, such as the case reported by Sari et al. (2019), in which the mini mental test (MMT) for forgetfulness was performed, whose patient's score was 11/30 and the Frontal Assessment Battery (FAB) test for frontal executive function, whose score was 9/18. In addition, the patient failed to complete the trail test and the score for the clock drawing test was 3/10.

The relationship between CADASIL and such psychiatric manifestations is not yet known, however, one of the explanations

is that multiple white matter infarctions, specifically in the frontal region, result in the disruption of the cortical-subcortical network, which leads to a change in the perception of reality and psychotic symptoms appear. Furthermore, there are studies that show the NOTCH signaling pathway is involved in neurodevelopment (Mishra et al., 2018).

With regard to neurological manifestations, these are usually the most frequent. Among the most common were migraines or headaches, with or without an aura, and. One of the cases had shown a unilateral headache, pulsatile, with an intensity of 8/10 associated with vomiting, accompanied by photophobia, phonophobia, in addition to episodes of seizures, although seizures are an uncommon symptom in CADASIL, being found in only 6 to 10% of the patients. Physical examinations showed decreased potency (0/5), increased tone on the right side of the arm and positive Babinski sign on the right side. In other cases, by Paraskevas et al. (2018), a patient's headache occurs from an early age, with throbbing and unilateral headaches lasting 24 hours and severe intensity (9/10) since age 16 years old (Anamnart et al., 2019; Ameer et al., 2021).

Ataxia is another not common manifestation, which leads to gait changes. Park et al. (2020), presented a patient whose truncal ataxia was greater than limb ataxia, which shows possible greater involvement of the cerebellar vermis than its hemisphere, or possible involvement of the dentate nucleus. His ataxia was accompanied by dysarthria, dysmetria, and dysdiadochokinesia, concluding as cerebellar involvement. The author also suggests acetazolamide as a form of treatment, as it causes vasodilation, and thus increases blood flow to the brain.

Other reports with more atypical manifestations are those observed by Schiess et al. (2018), with presentation of bilateral reduction of vibration sensation, deep and fast tendon reflex (+3), tandem gait and urinary incontinence. And Sakiyama et al. (2018) reported patients with symptoms of weakness in the legs and upper limbs, numbness in the bilateral fourth and fifth toes, difficulty walking, decreased deep tendon reflexes in the triceps and brachioradialis and absent reflexes in the knees and ankles.

Regarding vascular manifestations, there were some more dated manifestations besides the classic subcortical infarcts, such as a history of stroke, mainly the ischemic type, hypertension and especially vasculitis. On the other hand, the most severe cases were responsible for causing stenosis, as demonstrated by Zhang and Zhang (2019) with a case of intracranial atherosclerotic stenosis of the right middle cerebral artery with intraplaque hemorrhage (Sweeney, 2018; Motolese et al., 2020; Rajendran et al., 2021).

Furthermore, in the study by He et al. (2020), the proband performing Doppler US showed left carotid atherosclerosis, while his echocardiogram revealed ventricular septal hypertrophy and left atrial enlargement, along with the classic manifestations of MRI with diffuse white matter hyperintensities with multiple lacunar infarcts. In addition, her MRI angiography also revealed stenosis of the intracranial arteries, with cerebral arteriosclerosis, which showed a history of ischemic stroke, hypertension, gait ataxia and cognitive impairment.

In the case of a 61-year-old female patient, she had an initial blood pressure of 167/81 mmHg, anterior ST-segment elevation ECG with high troponin. His echocardiogram suggested SCAD (spontaneous coronary artery dissection) due to the abnormal appearance of his middle anterior descending artery, with tubular stenosis, which led to myocardial infarction, causing angina and dizziness. The mechanism behind these findings lies in the fact that in CADASIL an arteriopathy occurs with degradation of the coronary artery wall and greater risks of intramural compressive hematoma and ischemia (Tsanaxidis et al., 2019).

Jing et al. (2019) described in their study a 35-year-old patient with a transient ischemic attack of the spinal cord with anteromedian infarction of the cervical cord. It is theorized that this finding arises from the fact that vascular lesions generated by the NOTCH3 mutation have the potential for ischemic spinal vascular damage. The spinal cord is supplied by the anterior spinal artery (ASA), from the vertebral artery branches, and its terminal branches give rise to the commissural arteries, which, due to their smaller diameter, will be more susceptible to ischemic damage. Such pathophysiology explains spinal manifestations such as transient weakness of the lower limbs, which may even cause temporary paraplegia. It is worth mentioning that one of the treatments on that occasion was the use of antithrombotics.

Based on the cases found, it is worth noting the possible confusion that may occur between multiple sclerosis and CADASIL. In a study reported by Schiess et al. (2018), the patient's lumbar puncture demonstrated 10 oligoclonal bands. In neuroimaging exams, there was global atrophy and white matter lesions, which led to an immunomodulatory treatment, based on the fake hypothesis that the

patient would have had multiple sclerosis and CADASIL concomitantly.

However, findings of immunological alterations, such as oligoclonal bands in CSF, are not common in CADASIL. So immune findings in this genetic disease can be explained by the possibility of breaking the blood-brain barrier by the damage to brain vessels or directly by ischemic damages. Such conditions expose the immunologically privileged brain tissue and may induce an autoimmune process, which would explain the findings of oligoclonal bands. Despite these findings, there is no evidence of the coexistence of multiple sclerosis and CADASIL, which requires genetic and neuroimaging analysis to perform differential diagnosis (Schiess et al., 2018; Carone, 2016).

Another rarer report in the studies analyzed was peripheral neuropathy associated with CADASIL. In the proper study, the proband showed deposition of GOM in the wall of small endoneural vessels in the peripheral nerve, which would explain the neuropathies, while the electrophysiological study showed multiple mononeuropathy, with undetectable CMAP(Compound muscle action potentials) and SNAP (sensory nerve action potentials) in the left ulnar nerve. The explanation for this lies in the process of capillary damage characteristic of CADASIL with the potential for ischemia that will affect peripheral nerves by reduction of blood flow (Sakiyama et al., 2018).

Finally, an atypical case was diagnosed with CADASIL, but with manifestations of upper limb dystonia, parkinsonian syndrome with resting tremor and a history of stroke. The explanation for such findings suggests that vessel damage may have affected the striatonigral or thalamocortical pathway. In the meantime, cases of stroke are usually related to manifestations of dystonia, as long as it affects the corticothalamic circuit. Such findings led the author to consider CADASIL during the differential diagnosis of secondary dystonia (Spagnolo et al., 2021).

There is no official treatment for CADASIL, so all of them are more symptomatic, in order to ensure a better quality of life for the patient. Many of these drugs such as sodium valproate, phenytoin were used to treat seizures, losartan for vascular manifestations, sertraline for depression manifestations, paracetamol for severe headaches and IFN-beta-1a and fingolimod for patients with neuroinflammatory presentations that were confused with multiple sclerosis. Nevertheless, such case reports were not followed up to register the effectiveness of such drugs in the patients (Sari et al., 2020; Dunphy et al., 2019; Carone, 2016).

4. Conclusion

To conclude, the complexity of CADASIL is perceptible, and although it has a genetic cause (NOTCH3), cases of associations with other diseases, such as COVID-19, have been recorded. Due to its genetic component, familial cases are quite common, and can be manifested in both hetero or homozygous. Its manifestations present a range of variety, starting from psychiatric alterations with the formation of mental disorders, neurological alterations with the classic presentation of headache and seizures, and less common manifestations such as ataxia and hemiplegia, and vascular manifestations, such as stroke, vasculitis and stenosis of cerebral arteries. These presentations are marked by imaging tests that reveal white matter hyperintensity and cerebral infarctions.

Furthermore, manifestations of paraplegia induced by transient ischemic attack, presentations of dystonia and records of autoimmune reaction linked to CADASIL show the complexity of this disease and its diverse mechanisms of action from the modification of a single gene. Thus, it is necessary further studies in the area, in order to understand the pathophysiology that explains this great diversity of clinical alterations, as well as the rare findings related to CADASIL. Such studies will certainly improve the knowledge and may help the development of new and better treatments for those affected by this disease.

References

Ameer, M. A., Bhutta, B. S., Asghar, N., Haseeb, M. T., & Abbasi, R. N. (2021). Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL) Presenting as Migraine. *Cureus*, 13(5), e15355.

Anamnart, C., Songsaeng, D., & Chanprasert, S. (2019). A large number of cerebral microbleeds in CADASIL patients presenting with recurrent seizures: a case report. *BMC Neurol.*, 19 (106).

André, C. (2010). CADASIL: pathogenesis, clinical and radiological findings and treatment. *Arq. Neuro-Psiquiatr.*, 68(2), 287-299.

Carone, D. A. (2016). CADASIL and multiple sclerosis: A case report of prolonged misdiagnosis. *Applied Neuropsychology: Adult.*, 24 (3), 294-297.

Chen, B. S., Cleland, J. C., King, R. I., & Anderson, N. E. (2018). Cadasil presenting with focal and generalised epilepsy due to a novel NOTCH3 mutation. *Journal of Neurology, Neurosurgery & Psychiatry*, 89 (6), 36-38.

Correia, N. M. (2011). *SÍNDROME CADASIL: EPIDEMIOLOGIA, CLÍNICA E GENÉTICA* (Unpublished doctoral dissertation). Universidade do Porto, Porto.

Dunphy, L., Rani, A., Duodu, Y., & Behnam, Y. (2019). Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) presenting with stroke in a young man. *BMJ Case Rep.*, 12(7), e229609.

Ebihara, Y., Mochizuki, H., Ishii, N., Mizuta, I., Shiomi, K., Mizuno, T., & Nakazato, M. (2018). A Japanese Case of CADASIL with a Rare Mutation in Exon 24 of the NOTCH3 Gene. *Intern Med*., 57(20), 3011–3014.

Ferrante, E. A., Cudrici, C. D., & Boehm, M. (2020). CADASIL: new advances in basic science and clinical perspectives. *Curr Opin Hematol.*, 26 (3), 193-198.

Ganesan, D. N., Coste, T., & Venketasubramanian, N. (2021). Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) − Still to be Considered in the Presence of Vascular Risk Factors. *Case Rep Neurol*, 12 (1), 196-201.

He, J., Li, H., Sun, Y., Chen, M., Wang, L., Zhu, Y., Zhang, C. (2020). Homozygous NOTCH3 p.R587C mutation in Chinese patients with CADASIL: a case report. *BMC Neurology*, 20(72).

Jing, X. Z., Jiang, W., Gan, L., Zhu, W. A., Dong, M., & Yu, P. (2019). CADASIL with spinal cord involvement: a case report and literature review. *Journal of Neurology*, 266 (9), 2330-2333.

Joshi, S., Yau, W., & Kermode, A. (2017). CADASIL mimicking multiple sclerosis: The importance of clinical and MRI red flags. *Journal of Clinical Neuroscience*, 35, 75-77.

Jouvent, E., Alilli, N., Hervé, D., & Chabriat, H. (2020). Vanishing White Matter Hyperintensities in CADASIL: A Case Report with Insight into Disease Mechanisms. *Journal of Alzheimer's Disease*, 78 (3), 907-910.

Lahkim, M., Laamrani, F. Z., Andour, H., Gharbaoui, Y., Sanhaji, L., & El-Fenni, J. (2021). Cadasil syndrome: A case report with a literature review. *Radiol Case Rep.*, 16 (11), 3540-3543.

Lorenzi, T., Ragno, M., Paolinelli, F., Castellucci, C., Scarpelli, M., & Morroni, M. (2017). CADASIL: Ultrastructural insights into the morphology of granular osmiophilic material. *Brain Behav.*, 7 (3), e00624.

Motolese, F., Rossi, M., Gangemi, E., Bersano, A., Scelzo, E., Lazzaro, V. D., & Capone, F. (2020). CADASIL as Multiple Sclerosis Mimic: A 48-year-old man with severe leukoencephalopathy and spinal cord involvement. *Multiple Sclerosis and Related Disorders*, 41, 102014.

Mishra, D. K., Kishore, A., & Niranjan, V. (2018). CADASIL syndrome (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) presenting as psychosis. *Gen Psychiatr.*, 31 (3), e100017.

National Organization for Rare Disorders (NORD). (2021). CADASIL. https://rarediseases.org/rare-diseases/cadasil/.

Paraskevas, G. P., Constantinides, V. C., Yapijakis, C., Kararizou, E., Napaki, E. N., & Bougea, A. (2018). Recognition of Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) in Two Oligosymptomatic Sisters with Low CADASIL Scale Scores and a Venous Dysplasia: Report of a Novel Greek Family. *Journal of Stroke and Cerebrovascular Diseases*, 27 (9), 191-195.

Park, D. G., Min, J. H., Sohn, S. H., Sohn, Y. B., & Yoon, J. H. (2020). Ataxia Associated with CADASIL: a Pathology-Confirmed Case Report and Literature Review. *The Cerebellum*, 19 (6), 907-910.

Rajendran, I., Natarajan, M. D., Narwani, P., Alzouabi, O., Kawafi, K., & Khanna, N. (2021). A case of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) presenting as post-infectious manifestation of SARS-CoV-2 infection. *BJR Case Rep.*, 7 (3).

Sakiyama, Y., Matsuura, E., Maki, Y., Yoshimura, A., Ando, M., Nomura, M., Shinohara, K., Saigo, R., Nakamura, T., Hashiguchi, A., & Takashima, H. (2018). Peripheral neuropathy in a case with CADASIL: a case report. *BMC Neurol*., 18 (1), 134.

Saleem, S., Anwar, A., Abbasi, Z., Anjum, Z., & Tariq, Z. (2019) Periventricular Hyperintensities Mimicking Multiple Sclerosis. *Cureus*, 11 (8), e5326.

Sari, U. S., Kisabay, A., & Batum, M. (2019). CADASIL with Atypical Clinical Symptoms, Magnetic Resonance Imaging, and Novel Mutations: Two Case Reports and a Review of the Literature. *Journal of Molecular Neuroscience.*, 68 (4), 529-538.

Schiess, N., Huether, K., Szolics, M., Agarwal, G., El-Hattab, A. W., & Sathe, S. (2018). Multiple sclerosis or "inflammatory CADASIL?": Case Report and review of the literature. *Clinical Neurology and Neurosurgery*, 173, 196-199.

Spagnolo, F., Pinto, V., Rini, A. M., & Passarella, B. (2021). Dystonia and parkinsonism as presenting CADASIL features: a case report. *Neur. Science*, 42, 4781–4783.

Sweeney, B. J. (2018). Acute Simultaneous Multiple Diffusion-Weighted MRI Abnormalities in a Patient With CADASIL. *Headache: The Journal of Head and Face Pain*. 58 (5), 744-745.

Tsanaxidis, N., Elshafie, S., & Munir, S. (2019). Spontaneous coronary artery dissection in a patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy syndrome: a case report. *Eur Heart J Case Rep*., 3 (3).

Uppal, M., Kanellopoulos, D., & Kotbi, N. (2020). CADASIL presenting as late-onset mania with anosognosia. *Clin Case Rep*., 8 (1), 47-50.

Zhang, C., & Zhang, Z. (2019). CADASIL with Large Intracranial Arterial Atherosclerotic Stenosis. *Radiology*, 292 (3), 538.