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REVIEW **DERLEME**

CADASIL: WHAT'S NEW?

Özlem KAYIM YILDIZ

Cumhuriyet University Faculty of Medicine, Department of Neurology, Sivas, TÜRKİYE

ABSTRACT

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common form of hereditary cerebral small vessel disease. During the last years, our understanding of the disease has substantially changed due to increased availability of the genetic test and high-quality studies. Besides the classical CADASIL phenotype characterized by early onset stroke and premature dementia and death, milder forms with elderly onset have been recognized. On the other hand, atypical NOTCH3 mutations with unknown pathogenicity including cysteine sparing ones, in conjunction with milder forms of the disease make it difficult to ascertain the diagnosis in certain cases. In this paper, I have reviewed the recent data regarding the molecular diagnosis, neuroimaging findings and management of patients with CADASIL.
Keywords: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL, magnetic resonance imaging, NOTCH3 mutation, management, treatment.

CADASIL: SON GELİŞMELER NELER?

ÖZ

Subkortikal infarktlar ve lökoensefalopatiyle birlikte serebral otozomal dominant arteriopati (CADASIL) herediter serebral küçük damar hastalıkları içerisinde en yaygın olanıdır. Son yıllarda genetik testlerin yaygınlaşması ve yüksek kaliteli çalışmalar sayesinde hastalıkla ilgili bilgilerimizde önemli değişiklikler olmuştur. Erken başlangıçlı inme ve prematür demans ve ölümle karakterize klasik fenotipin yanı sıra daha ileri yaşta başlangıç ve daha hafif seyir özellikleri gösteren formlar da belirlenmiştir. Öte yandan sistein koruyan mutasyonlar gibi patojenitesi bilinmeyen atipik NOTCH3 mutasyonlarının saptanması belirli vakalarda tanıyı güçleştirmektedir. Bu gözden geçirme yazısında CADASIL'in moleküler tanısı, nörogörüntüleme bulguları ve CADASIL hastalarının yönetimi ile ilgili son verileri derledim.
Anahtar Sözcükler: Subkortikal infarktlar ve lökoensefalopatiyle birlikte serebral otozomal dominant arteriopati CADASIL, manyetik rezonans görüntüleme, NOTCH3 mutasyonu, yönetim, tedavi

Address for Correspondence: Prof. Özlem Kayım Yıldız, M.D. Cumhuriyet University Faculty of Medicine, Department of Neurology, Sivas, Türkiye.
Phone: +90346 258 00 00 **E-mail:** ozlemkayim@cumhuriyet.edu.tr
Received: 24.12.2023 **Accepted:** 23.01.2024
ORCID ID: Özlem Kayım Yıldız 0000-0002-0382-9134.
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1. INTRODUCTION

Approximately 25% of strokes are lacunar strokes and deep intracerebral hemorrhages resulting from cerebral small vessel disease (CSVD) (1). CSVD is the main pathology underlying vascular cognitive impairment (2). Rare monogenic hereditary diseases constitute a small portion of sporadic CSVD, which occurs mostly in relation to conventional vascular risk factors (3). Rare monogenic diseases are involved in 1.5% of patients with young-onset lacunar strokes (3).

The most common hereditary CSVD is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (3). The prevalence is believed to be 2-5 per 100.000 for classical presentation (4). Epidemiologic differences between populations are likely (4-7). However, it should be kept in mind that there are also undiagnosed patients, and the actual prevalence may be higher.

2. PATHOLOGY

NOTCH3 mutations lead to CADASIL (8). NOTCH3 is expressed in vascular smooth muscle cells in adults and maintains vascular contractility (9). CADASIL mutations impair the clearance of the extracellular portion of NOTCH3 (9). The degradation product of the 210-kDa Notch3 extracellular portion accumulates in the cytoplasmic membrane and pericytes of vascular smooth muscle cells and smooth muscle cells degenerate (9). There is intense Notch3 immunoreactivity in vascular smooth muscle cells and pericytes of capillaries (9). Granular osmophilic material (GOM) accumulates around small penetrating arteries in the brain (10).

Although the exact mechanism of lacunar infarcts is unknown, hemodynamic disturbance of arterioles and loss of compliance and autoregulation are suggested to be the cause. (11). It is thought that the involvement of pericytes may lead to impaired cerebral microcirculation and defective vasomotor reactivity (12,13).

NOTCH3 is widely present in vascular smooth muscle cells. This leads to the question of why the clinical manifestations associated with CADASIL are confined to the brain. In fact, GOM is also present in vascular smooth muscle cells in muscle, skin, and most visceral organs (14,15). Furthermore, reports of peripheral vascular dysfunction, and cardiovascular and renal involvement in CADASIL patients are also available (16-20). The proposed mechanism for the phenotype to be characterized by predominant cerebral involvement is that in CADASIL, mural cells and pericytes are more prone to apoptotic stress, making the pathological process overt in the brain (21).

3. 3. CLINICAL CHARACTERISTICS

The classic CADASIL phenotype includes migraine, recurrent lacunar strokes, cognitive impairment, acute encephalopathy, and gait and mood disorders (22).

3.1. Migraine

Migraine is one of the earliest features of CADASIL, reported in approximately 75% of patients (23-26). It is more prevalent in women (26). The median age of onset is 28 years (26). It frequently has aura and headache-free, complicated, and prolonged aura may be observed (23,27). The most commonly reported aura type is visual, with typical symptoms including scintillating scotom, visual field defects, phosphenes, and blindness (27). This is followed by sensory, language-related, and motor auras (27). Confusional aura also occurs (26).

Migraine attributed to CADASIL is well described in the 3rd edition of the International Classification of Headache. Accordingly, in a CADASIL patient diagnosed with a NOTCH3 mutation, GOM diagnosis by skin biopsy with immunostaining or GOM detection by electron microscopy, typical, hemiplegic or prolonged recurrent migraine attacks with aura occur as the first clinical manifestation of the disease and diminish or disappear with the development of other disease symptoms (28).

CADASIL encephalopathy, reported in approximately 10% of patients, is an acute reversible encephalopathy picture that occurs in the absence of another organic cause, lasts longer than 24 hours, and is associated with impaired consciousness (26,29). Fever, seizure, hallucinations, nausea, vomiting, and meningismus results may be present (26). These episodes usually last for days, resolve spontaneously and recurrence may occur (26). On electroencephalography, slowing of background

activity, increased protein in cerebrospinal fluid, and rarely pleocytosis may be observed; no lesion showing diffusion restriction is usually observed on brain magnetic resonance imaging (MRI) (26). Since it is approximately 5 times more common in migraine patients with aura and develops frequently after a migraine attack, it is considered that its pathogenesis may be related to migraine (26).

The physiological relationship between CADASIL and migraine is not clear; it is hypothesized that migraine-associated cortical spreading depression is a natural protective strategy to help cerebral vasoactivity (30). Supporting the protective feature of migraine, it was reported that CADASIL patients with migraine had a lower risk of stroke and fewer cerebral microbleeds than those without migraine; however, this result was not confirmed in a series of 914 patients, and migraine diagnosis was more frequent in CADASIL patients with stroke (31,32).

3.2. Neuropsychiatric Symptoms

Neuropsychiatric manifestations include mood and behavioral disorders and varying degrees of cognitive impairment (33). The reported prevalence of mood disorders varies between 7 and 50% (33). It usually develops between the ages of 30-60, after the first stroke, and in the presence of a certain level of cognitive impairment (34). Its severity is variable. Approximately half of the patients have emotional disorders characterized by anger, irritability, and emotional incontinence (35). Although depression and anxiety disorders leading to suicide attempts are more frequent, hypomanic and manic episodes and alternating mood changes compatible with dysthymic or bipolar disorder may also develop (33). Apathy, which is usually associated with cognitive impairment, is common (36).

The spectrum of cognitive impairment in CADASIL ranges from moderate cognitive slowing to impairment in executive functions and overt dementia affecting all cognitive domains (25,37). In the early period, cognitive functions slow down, then attention, memory and executive dysfunctions are observed, while visual-spatial abilities and reasoning deteriorate over time (37). Initially, memory is relatively preserved (33). The course of cognitive impairment is not linear and occurs mainly after the age of 50 (38). Dementia usually develops over the age of 60 (37). In the last stage of the disease, usually around the age of 70, mutism and bedriddenness develop (33).

3.3. Stroke

Lacunar strokes are a characteristic feature of CADASIL, but intracranial and extracranial vascular abnormalities and intracerebral hemorrhage were also reported (32,39-41). In a series of 914 patients, it was reported that approximately 90% of patients had at least one documented ischemic stroke, approximately 28% had at least one episode of transient ischemic attack and approximately 6% developed hemorrhagic stroke (32). Intracerebral hemorrhage is a common presentation of CADASIL in Asia, reported in 36% of patients (42).

3.4. Disease Course

Prospective data on the natural history of CADASIL patients are limited. In 1999, Desmond et al. (24) reported that the mean age at first stroke was 41.2 years and the mean age at death was 54.8 years in a series including 105 patients. Davous et al. (43) reported that the mean age at first stroke was 43.9 years and the mean age at death was 56.7 years in a series including 134 patients (43). In a series of 411 patients published in 2004, the median age at first stroke was 50.7 years in men and 52.5 years in women; the median age at unassisted walking was 58.9 years in men and 62.1 years in women; the median age at bed dependency was 62.1 years in men and 66.5 years in women; and the median age at death was 64.6 years in men and 70.7 years in women. Although the age of reaching all adverse outcomes was earlier in men than in women, this difference did not reach statistical significance for the age at first stroke (44). According to a recently published study involving 914 patients, the median age at first stroke is 56 years in men and 58 years in women, and the mortality rate is significantly higher in men (32). The incidence of stroke was determined as 10.4/100 person-years (45).

A possible explanation for the increase in the reported ages of stroke onset and death over the years is the widespread use of genetic testing in recent decades, leading to the diagnosis of patients with milder prognosis and older age of onset.

4. 4. NEUROIMAGING

Brain MRI is critical in the diagnosis of CSVD. The necessity for genetic testing is largely based on MRI results (46). Typical brain MRI results of hereditary CSVD include diffuse, symmetrical, and progressive white matter hyperintensities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, multiple acute or chronic lacunar infarcts, dilated perivascular spaces, and cerebral microbleeds and brain atrophy on T2* gradient recall echo or susceptibility-weighted images (47). For a long time, it was believed that the presence of white matter hyperintensities affecting the anterior temporal poles, frontal lobes (subinsular areas and superior frontal gyri), and periventricular area had a high discriminatory power for CADASIL from sporadic subcortical arteriosclerotic encephalopathy and was sufficient to request genetic testing (48). However, temporal white matter hyperintensities can also be observed in other hereditary CSVD, sporadic CSVD, and other diseases (46,49-51). Since recent studies have shown that certain MRI results considered specific for CADASIL have a low positive predictive value, it can be said that the discrepancy between risk factors and lesion load rather than a specific imaging result may be a guide for genetic testing (46). However, it is also possible that milder phenotypes may be missed with this approach (46). Dilated periventricular spaces, especially at the junction between the cortex and subcortical white matter, are frequent results (46,52). Although rare in sporadic CSVD, corpus callosum lesions may be observed in CADASIL (53). In contrast to sporadic CSVD, the load of white matter hyperintensities is not correlated with disease severity or clinical worsening (46,54,55).

Lacunar infarctions in the subcortical white matter are one of the key imaging results of CADASIL (46). Infarcts are not limited to white matter, postmortem 7-T MRI showed cortical infarcts that were not identified on 1.5-T MRI (56). Lacunar infarctions showing diffusion restriction without acute stroke presentation were reported (57). Although the absence of diffusion restriction is typically expected during CADASIL encephalopathy, association with acute lacunar infarction was rarely reported (46). In contrast to white matter hyperintensities, both the number and volume of lacunar infarcts are associated with disease severity (54,58). Brain atrophy is also one of the imaging results that accounts for the variability in clinical deterioration (55).

Cortical superficial siderosis is not observed in CADASIL (59). Microbleeds, especially in the thalamus, basal ganglia, and pons, are a common result (60). Although microbleeds are not associated with disease severity, microbleeds in the brainstem and the presence of more than 10 microbleeds in total were reported to be independently associated with intracerebral hemorrhage (46,61). Figure 1, 2 and 3 shows brain MRI results in a genetically confirmed CADASIL case followed up in our clinic. Figure 1 shows signal changes showing confluence in subcortical and periventricular white matter, lacunar infarcts, involvement of external capsula and anterior lobe. Figure 2 shows corpus callosum involvement. Figure 3 shows acute lacunar infarction with diffusion restriction in CADASIL encephalopathy.

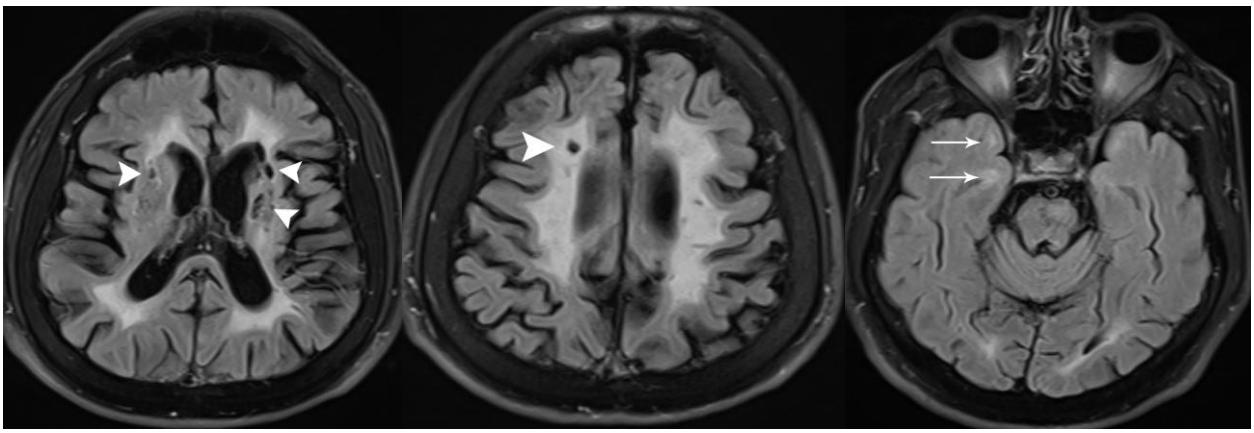

Figure 1. A, B and C. Brain MRI. Axial FLAIR. Hyperintense signal changes showing confluence in the subcortical and periventricular white matter, lacunar infarcts (arrowhead). The external capsule was retained. 1C. Mild subcortical hyperintense signal change in the anterior temporal lobe (arrow).

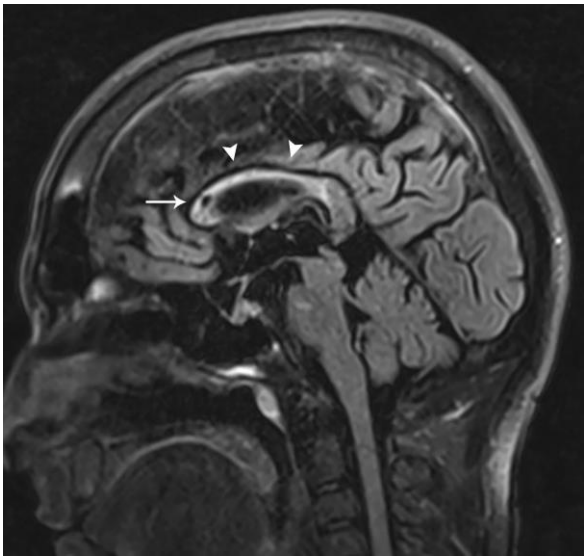

Figure 2. Brain MRI. Sagittal FLAIR. Atrophy in the corpus callosum, hyperintense signal change with relative preservation of the splenium (arrowhead), and lacunar infarction in the genu (arrow).

5. GENETICS

NOTCH3 with 33 exons encodes the single-pass transmembrane Notch3 receptor, which plays an important role in the differentiation and maturation of vascular smooth muscle cells (8). Exons 2-24 of the NOTCH3 gene encode 34 epidermal growth factor-like repeats (EGFr) in the extracellular portion (11). Each EGFr contains 6 cysteine residues forming 3 disulfide bonds stabilizing the Notch6 receptor. Mutations that reduce the number of cysteines in EGFRr from double to single cause abnormal disulfide bridge formation, disrupting the structure of the extracellular portion of the Notch3 receptor and leading to its misfolding and aggregation (9, 62). To date, over 200 cysteine-related mutations have been reported, most of which are single nucleotide changes. Most mutations are missense mutations, that is, they are characterized by the substitution of wild-type cysteine with another amino acid (11,63).

5.1. Atypical Mutations

In addition to missense mutations, duplication and deletion mutations that change the number of cysteine residues were also reported (11). However, there are reports that mutations that do not change cysteine number (sparing) may also lead to CADASIL pathology (11,64-67). There

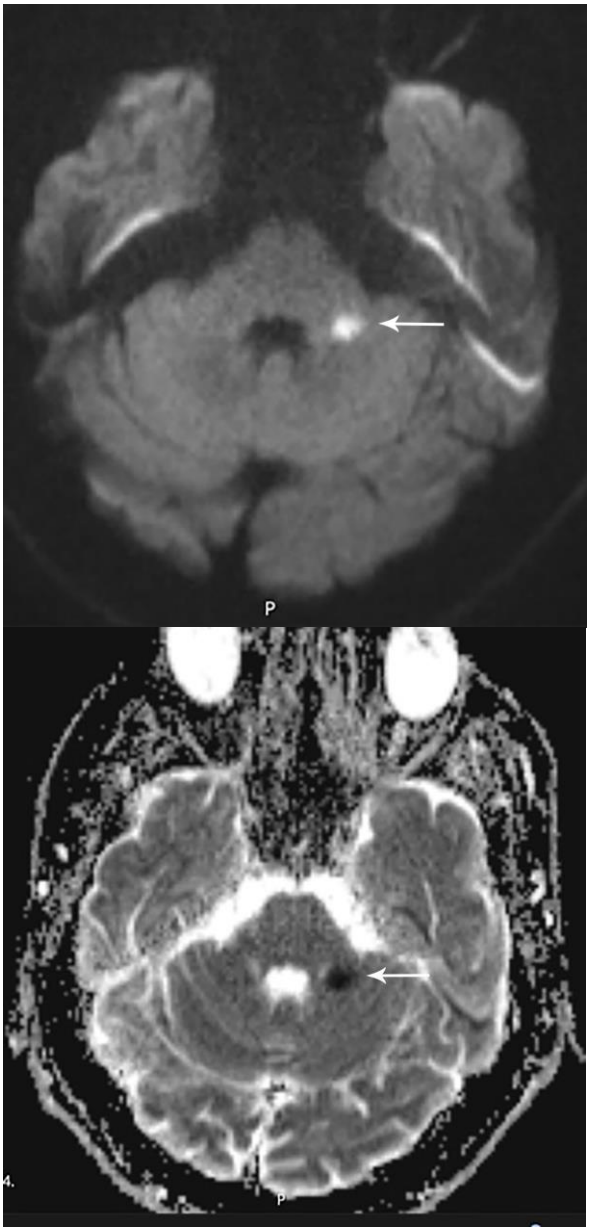

Figure 3. Brain MRI. A. DWI and B. ADC. Acute lacunar infarction (arrow) showing diffusion restriction in the left middle cerebellar peduncle during CADASIL encephalopathy.

are also cases of CADASIL resulting from homozygous mutations, and although it was suggested that the clinical phenotype may be more severe in these cases, this result was not consistently demonstrated (11,68).

5.2. Genotype-Phenotype Correlation

There are studies showing that certain mutations are associated with many clinical

features such as stroke, immobilization, and age at death (44). However, some authors associate the differences in phenotype with environmental risk factors and report that no genotype-phenotype relationship was found (23).

Mutation localization may also be a determinant of disease severity. Patients with mutations in the EGFr 1-6 region have an earlier age of onset of stroke, shorter survival, and higher white matter hyperintensity volume compared to patients with mutations in the EGFr 7-34 region (69). In CADASIL patients, NOTCH3 mutations occur mostly in the EGFr 1-6 region (69). Pathogenic variants are concentrated in the EGFr 7-34 region in the general population, and it is possible for these patients with a lower MRI lesion load to be diagnosed with sporadic CSVD (69,70). Therefore, EGFr 1-6 variants are associated with the classic, more severe CADASIL phenotype. Mutations in the EGFr 7-34 region may be associated with milder phenotype and non-penetrance.

Reduced penetrance and variability of the phenotype spectrum in individuals with the same variant may be related to other genetic determinants, comorbidities, and environmental factors (71). The variability of the phenotype makes it difficult to determine the pathogenicity of some mutations, especially those that do not alter the cysteine number.

6. DIAGNOSIS

6.1. Diagnostic Criteria And Patient Selection Before Genetic Testing

Due to the high cost and time-consuming nature of genetic testing, a number of diagnostic criteria were proposed to predict the need for testing. The first one was developed by Davous et al. (72) in 1997. These criteria require an early age of onset for diagnosis, stroke-like episodes leading to clinically persistent neurological deficits, migraine, major mood changes, and subcortical dementia, family history indicating autosomal dominant inheritance, absence of vascular risk factors, and presence of typical brain MRI results and were proposed at a time when genetic testing was not yet widespread and individuals with atypical features of the disease were not recognized (72). However, they may have low sensitivity due to the detection of atypical cases by genetic testing and the demonstration that the CADASIL phenotype may vary between the presence of an asymptomatic mutation and severe involvement. With these initial criteria proposed by Davous et al. (72), patients with advanced age of onset, no family history, and concomitant cardiovascular risk factors may be missed.

In 2012, Pescini et al. (73) developed the CADASIL scale based on the clinical characteristics of 536 patients from many countries and the neuroimaging results of 435 patients (Table 1, 73). The authors reported the sensitivity and specificity of the scale as 96.7% and 74.2% for the definitive diagnosis of CADASIL (73).

Table 1. CADASIL scale.

Migraine	1
Migraine with aura	3
TIA or stroke	1
TIA/stroke before age 50	2
Psychiatric disorders	1
Cognitive impairment/dementia	3
leukoencephalopathy	3
Leukoencephalopathy extending to the temporal lobe	1
Leukoencephalopathy extending to the external capsule	5
Subcortical infarcts	2
Family history in at least one generation*	1
Family history in at least two generations*	2

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy); TIA: transient ischemic attack. Total score 0-25. A score ≥ 15 supports the diagnosis of CADASIL. *There must be at least one of the following: headache, transient ischemic attack/stroke, cognitive impairment and psychiatric disorder. Modified from reference-73.

Mizuta et al. (74) proposed diagnostic criteria based on the results of 102 patients in Japan, which have a sensitivity of 97% with a specificity of 7.5% and can be used to identify patients requiring genetic testing (Table 2). In the same population, the sensitivities of the Davous criteria (72) and CADASIL scale (73) were 52% and 52.1%, respectively, raising questions about whether these criteria are adaptable to different populations (74).

In addition to these criteria, triage based on skin biopsy and brain MRI results was also proposed (75). Moderate or severe involvement of the anterior temporal pole on MRI has been reported to have 89% sensitivity and 86% specificity for diagnosis, while involvement of the external capsule has 93% sensitivity and 45% specificity (75). The sensitivity and specificity of skin biopsy were found to be 45% and 100%, respectively (75). Currently, skin biopsy is a less commonly used diagnostic method, but it can be used to clarify the diagnosis when a mutation of

unknown or unclear significance is determined (76). The accuracy of biopsy can be improved using immunohistochemistry (77).

Table 2. CADASIL diagnostic criteria suggested by Mizuka et al. (74).

1. Age of onset (clinical symptoms or white matter lesions) ≤ 55 years
2. At least two of the following clinical findings:
a. Subcortical dementia, long tract findings or pseudobulbar palsy
b. Stroke-like episode with focal neurological deficit
c. mood disorder
d. Migraine
3. Autosomal dominant inheritance
4. White matter lesions in the anterior temporal pole on MRI and CT
5. Exclusion of leukodystrophy
Genetic criteria
2-24, which leads to gain or loss of cysteine residues in EGFr. NOTCH3 mutations localized to exons. Cysteine-sparing variants should be carefully evaluated by skin biopsy or segregation studies.
Pathological criteria
The pathological finding of CADASIL is GOM detected by EM. Immunostaining of the NOTCH3 extracellular portion is also useful.
Certain
1. White matter lesions on MRI or CT
2. Clinical criterion 5
3. Genetic criteria and/or pathological criteria
Possible
1. All clinical criteria are met
Potential
Abnormal white matter lesions (Fazekas grade ≥ 2) and all of the following:
1. Age of onset ≤ 55 years
2. At least one of the symptoms in clinical criterion 2

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy); MRI: magnetic resonance imaging; CT: computed tomography; EGFr: epidermal growth factor-like repeats; EM: electron microscopy; GOM: granular osmophilic material. Modified from reference 74.

In conclusion, a family history of unexplained periventricular white matter lesions, migraine, stroke, mood disorders, or dementia should raise suspicion for the diagnosis. However, the absence of family history, onset at an advanced age, and presence of vascular risk factors do not exclude the diagnosis. The American Heart Association recommends that patients with stroke associated with small vessel occlusion before age 55 years without vascular risk factors or a family history of CADASIL should be evaluated for genetic analysis (78).

6.2. Diagnostic and Predictive/Presymptomatic Genetic Testing

Although there is no curative treatment option for CADASIL, prevention of vascular risk factors may modify the disease course (71). Molecular diagnosis is therefore necessary. It should be recognized that there may be difficulties in interpreting NOTCH3 mutation results due to variable results such as cysteine-free mutations (66). The importance of the results for both patients and family members should not be neglected, and counseling should be provided before and after the test (79). It should be noted that the conditions for ordering a diagnostic test for people with clinical symptoms and a predictive or presymptomatic test for asymptomatic family members are different. It should be kept in mind that the penetrance of NOTCH3 variants is incomplete and may vary. For predictive or presymptomatic testing, it is recommended to use the ethical and practical recommendations used in Huntington's disease, another autosomal dominant disease (80).

In symptomatic individuals, having a known pathogenic NOTCH3 mutation in a family member simplifies the testing process because there is only one mutation to investigate. If the mutation is unknown, more complex analyses should be performed; the general approach is targeted testing starting with common variants in the more commonly affected EGF fragments and then proceeding to the sequence of the whole exon/gene. If the patient has more than one prediagnosis of cerebral small vessel disease, genetic panels may be considered.

7. TREATMENT

7.1. Management of Environmental Factors

The prevalence of modifiable vascular risk factors in CADASIL varies depending on the type of study, duration of follow-up, patient age, country, and the number of factors examined. In early studies, vascular risk factors were reported to be rare (24), but recent studies show that these factors are more common than thought (32, 74, 81). A possible reason for this finding is the tendency to order genetic testing for CADASIL in patients without early vascular risk factors.

Hypertension, hyperlipidemia, diabetes mellitus, peripheral vascular disease, and tobacco use were associated with the development of stroke, dementia, and disability in CADASIL patients (23,32,55,82). Cognitive reserve associated with educational level may modify cognitive dysfunction, at least early on, similar to neurodegenerative diseases (83).

No randomized trials investigated the effect of vascular risk factor management on clinical outcomes in CADASIL, but hypertension control and tobacco cessation should be recommended (78). There are no data on the management of hyperlipidemia (78). 2020 European Academy of Neurology guideline recommends that statins should not be given to patients with normal cholesterol levels, but states that statins are not contraindicated (76).

7.2. Antithrombotic Therapies and Acute Stroke Management

The role of antiplatelet therapy in CADASIL in protecting against recurrent ischemic stroke is unknown and there is no high-level evidence on its safety. Many CADASIL patients are treated with antiplatelets (84). Intracerebral hemorrhage may develop both in patients receiving and not receiving antithrombotic treatment (39). A large observational study showed that antiplatelet use in CADASIL patients had no significant effect on either ischemic stroke or intracerebral hemorrhage (85). The 2020 European Academy of Neurology guideline states that there is no evidence to support the use of antiplatelet agents in CADASIL patients without prior ischemic stroke (76). The 2023 American Heart Association guideline recommends against the use of antiplatelets for primary prophylaxis and states that low-dose aspirin may carry a low risk in patients with prior ischemic stroke (78).

Although anticoagulant-associated intracerebral hemorrhage is not common in CADASIL, the safety of anticoagulants is not clear. In a Taiwan series, it was reported that 5.9% (15/255) of patients had symptomatic intracerebral hemorrhage and 6.7% (1/15) of these were correlated with anticoagulant use (61). The 2020 European Academy of Neurology guideline states that oral anticoagulation is not contraindicated in patients with CHA2DS2-VASc score >2 and atrial fibrillation or other indications (76). In patients with both CADASIL and atrial fibrillation, left atrial appendage closure may be a reasonable alternative to long-term anticoagulation. This recommendation is particularly suitable for patients with a high CHA2DS2-VASc score and a high number of microbleeds (78).

Data on the efficacy and safety of thrombolysis and thrombectomy in CADASIL patients presenting with acute stroke are limited. There are reports of thrombolytic use without hemorrhagic complications (86). Without systematic study results, decisions on reperfusion or recanalization therapy should be made on an individual basis. The 2020 European Academy of Neurology guideline recommends that patients should not receive thrombolytic therapy in acute small vessel occlusion (76). The 2023 American Heart Association guideline recommends mechanical thrombectomy without thrombolytic therapy in the presence of acute stroke secondary to large vessel occlusion (78).

7.3. Migraine Treatment

In approximately half of the patients, migraine is severe and impairs quality of life (87). There are no randomized trials on the optimal treatment of migraine in CADASIL patients, and the impaired cerebral autoregulation associated with the disease raises concerns about the use of migraine medications in this patient population (88). The most commonly used abortive medication is simple analgesics and prophylactic medication is beta blockers (88). Among beta-blockers, propranolol is correlated with unfavorable clinical response (88). There are anecdotal reports that acetazolamide and sodium valproate may be useful (89,90). Although it was reported that acetazolamide may also improve cerebral hemodynamics in CADASIL patients, the 2020 European Academy of Neurology guideline states that there is no evidence to recommend the use of acetazolamide (76, 91). Migraine triggers in CADASIL patients are similar to those in other migraine patients and avoidance of triggers, good sleep, and exercise may be recommended. Information on abortive treatments is limited; there are reports on the safe use of triptans and the 2020 European Academy of Neurology guideline states that triptans are not contraindicated (26,76).

7.4. Treatment of Neuropsychiatric Symptoms

Optimal treatment for neuropsychiatric symptoms is not established, and usually, traditional pharmacotherapeutics such as selective serotonin reuptake inhibitors are used (33). In

the presence of concomitant cognitive impairment, tricyclic antidepressants with anticholinergic effect should be avoided (33). A randomized study with donepezil showed no overall benefit in cognition, but the benefit was found in many sub-scores indicating executive functions (92). There is anecdotal evidence that galantamine may be effective (93).

8. SPECIAL CONDITIONS

8.1. CADASIL and Pregnancy

There is insufficient data on the risks of CADASIL in the course of pregnancy, the postpartum period, or the fetus. In a study involving 93 pregnancies in 50 women in Italy, it was reported that the risk of complications did not increase during pregnancy, peripartum, or postpartum period (94). In Finland, a total of 43 completed pregnancies in 25 women were evaluated and it was reported that almost half of the patients had transient neurological symptoms such as hemiparesthesia, hemiparesis, aphasia, and visual disturbances, especially in puerperium (95). The 2020 European Academy of Neurology Guidelines states that antithrombotic use is not required during pregnancy (76). There is no evidence that vaginal delivery is unsafe. Similarly, there is no data on preterm complications in fetuses carrying NOTCH3 mutations

8.2. Perioperative Management of CADASIL

Systematic data on the perioperative management of CADASIL patients are not available. There is reasonable concern that disruption of cerebral autoregulation may increase the risk of perioperative stroke and delirium. Nevertheless, neuraxial (96) and general anesthesia (97) without postoperative stroke or delirium were reported. It was recommended that patients should be operated in centers with a stroke unit, intraoperative mean arterial blood pressure should be kept within the limits of cerebral autoregulation, normocapnia should be provided, head-down position that may impair venous return and sitting position that may decrease cerebral blood flow should be avoided (97,98).

8.3. CADASIL and Catheter Angiography

Most reports of cerebral angiography in CADASIL patients indicated that the blood vessels appear normal, but there may be mild distal changes (99). It was reported that 69% (11/16) of CADASIL patients who underwent cerebral catheter angiography had neurologic symptoms lasting hours to weeks (100). The 2023 American Heart Association guideline states that a clinical or genetic diagnosis of CADASIL should be considered a relative contraindication for cerebral catheter angiography; however, in acute stroke patients with acute large vessel occlusion, a catheter procedure can be performed for therapeutic, not just diagnostic, purposes (78).

9. CONCLUSION

In conclusion, our knowledge about CADASIL, the most common hereditary CSVD, has improved in the last decades. With the widespread use of genetic tests, it was determined that the disease has a later onset and milder form, and patients frequently have vascular risk factors. In addition, the increasing detection of mutations of uncertain pathogenicity and variable penetrance necessitates appropriate evaluation of genetic test results. Randomized controlled trials are required to determine sensitive and specific neuroimaging results that can provide triage for genetic testing and implement effective and safe treatments.

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Ethics

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