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Managing atherosclerotic carotid disease: treatment essentials

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Abstract

Atherosclerotic carotid disease (ACD) is a common etiology of stroke, demanding a comprehensive understanding of effective intervention. This review explores the pathophysiology and treatment strategies for ACD, as well as the diagnostic imaging findings. ACDs can cause ischemic strokes by different mechanisms including plaque rupture, embolism, and stenosis-induced hypoperfusion. Early intervention is vital to avert adverse outcomes. Medical management remains the first line of treatment in the form of antiplatelets, antihypertensives, and statins. While carotid artery stenting (CAS) has gained traction in the last few years, carotid endarterectomy (CEA) remains favored for asymptomatic cases in international guidelines. Current evidence has revealed that both CAS and CEA are reasonable options for symptomatic cases. Doppler ultrasound, computed tomography angiography, and magnetic resonance imaging are pivotal in diagnosing and characterizing ACD plaques. Plaque features, such as lipid-rich necrotic core, fibrous cap thickness, or intraplaque hemorrhage are essential in guiding the treatment.

Keywords: *Atherosclerotic. Carotid. Stroke. Stenosis. Plaque.*

Manejo de la enfermedad carotídea aterosclerosa: puntos esenciales para el tratamiento

Resumen

La enfermedad carotídea aterosclerosa (ACD, por sus siglas en inglés) es una etiología común de infartos cerebrales, requiriendo de comprensión integral para una intervención efectiva. Esta revisión explora la fisiopatología y estrategias de tratamiento para la ACD, así como los hallazgos diagnósticos por imagen. La ACD puede causar infartos cerebrales por diferentes mecanismos, incluyendo la rotura de placa, embolismo e hipoperfusión inducida por la propia estenosis. La intervención temprana es crucial para evitar resultados adversos. El manejo médico continúa siendo la primera línea de tratamiento en forma de antiagregantes plaquetarios, antihipertensivos y estatinas. A pesar de que la angioplastía carotídea con stent (CAS, por sus siglas en inglés) ha ganado popularidad en los últimos años, la endarterectomía carotídea (CEA, por sus siglas en inglés) sigue siendo preferida para casos asintomáticos según las guías internacionales. La evidencia actual

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ha demostrado que tanto CAS como CEA son opciones razonables para casos sintomáticos. La ecografía Doppler, la angiotomografía computarizada y la resonancia magnética son fundamentales para diagnosticar y caracterizar las placas de ACD. Las características de la placa, como lo son el núcleo necrótico rico en lípidos, el grosor de la capa fibrosa o la hemorragia intraplaca son esenciales para guiar el tratamiento.

Palabras clave: *Aterosclerosis. Carótida. Infarto cerebral. Estenosis. Placa.*

Introduction, background, and epidemiology

In 1951, Miller-Fisher published a seminal paper that described the symptoms and physiopathological substrate of atherosclerotic carotid disease (ACD), using the radiological evidence of 45 published cases[1]. Dr. Miller-Fisher concluded that this disease was much more frequent than previously thought and pointed out that, because of its location in the neck, atheroma plaques in carotids stood in a "no man's land" situation between pathology and neuropathology, and thus were not receiving the attention they warranted[1].

Today we know that carotid stenosis is responsible for up to 25% of ischemic strokes (IS) in the US[2]. In addition, it has been reported that 10-15% of all IS happen in the setting of ≥ 50% stenosis of the internal carotid artery (ICA)[3].

This sort of information is scarce in Mexico, with the Brain Attack Surveillance in Durango (BASID)[4] study and *Primer Registro Mexicano de Isquemia Cerebral* (PREMIER)[5], a registry, providing the most recent data. PREMIER noted a funnel effect at the end of its median follow-up of 358 days, with a third of the patients with an excellent outcome (modified Rankin Score [mRS] 0-1), another third with mRS 2-5, whereas the other third dead[5]; only 8% of all strokes were classified as large-artery atherosclerosis, and 0.1% and 0.5% of patients underwent carotid endarterectomy (CEA) and carotid artery stenting (CAS), respectively[5]. In a subanalysis of strokes of undetermined cause, 40% of those had evidence of two or more risk factors for large-artery atherosclerosis[5]. The investigators noted a very low use of the complete diagnostic tools to determine etiology because of limited resources[5]. BASID reported a prevalence of 5.1-7.7 strokes/1,000 persons in the Durango municipality, which is within the range of other door-to-door surveys in Latin America[4].

Historically, ACD has been classified according to the degree of stenosis, using either the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[6] or European Carotid Surgery Trial (ECST)[7] criteria. Between the two, NASCET has seen a wider use. However, there are more biomarkers for stroke risk than just the degree of stenosis[8].

Treatment options include medical treatment, CEA, and CAS, with the latter now employing transcarotid artery revascularization as an option to mitigate the risk of artery-to-artery embolism due to dislodged atheroma during the passage of the catheter over the aortic arch and the supraaortic arteries[9]. The decision for revascularization is greatly influenced by whether the stenosis is symptomatic, and the treatment of choice is determined by the patient's status (unilateral or bilateral stenosis, location and morphology of the plaque, vessel anatomy, and degree of stenosis). Most of the available evidence is on symptomatic stenosis and medical and surgical management. No doubt the data regarding ACD management has exploded in the last few decades, with an ever-growing body of evidence for CAS.

This review aims to provide a simple, treatment-oriented guide to the different situations the physician may find in a patient with ACD. Sections are organized into symptomatic and asymptomatic disease, and each one of these refers to each of the current treatment modalities according to international guidelines.

A systematic search was conducted on MEDLINE (PubMed), using the following Medical Subject Headings terms: (ACD) + (neuroimaging findings) + (revascularization techniques [either CEA or CAS]). We selected original articles, as well as clinical trials and review articles. Each article was read to completion, to check for other useful references. This paper will focus on ACD at the ICA, both symptomatic and asymptomatic, and its treatment modalities: medical, surgical, and neurointerventional.

Plaque formation

Atherosclerosis is a systemic disease, chronic and progressive, characterized by a constant state of inflammation and cholesterol plaque formation with different degrees of hemodynamic repercussion in the affected arteries[10]. Carotid atherosclerosis has been identified as a surrogate for systemic atherosclerosis in a subclinical stage and a predictor of cardiovascular events, such as

coronary disease and IS[10]. Because of this, the current management of ACD is focused on detecting the plaque in a timely manner, early recognition of intimal thickening, and the degree of occlusion as markers of ACD[10]. In this line of thought, it is now known that ACD will cause IS by one of these two mechanisms: (1) plaque rupture and thrombosis with subsequent artery-to-artery embolism, and (2) flow-reducing stenosis.

Some risk factors such as being male, overweight, hypertension, diabetes, and smoking have been linked to ACD. Hypertension has the most remarkable correlation to the early stages of this disease[11].

The most common site for plaque formation in the cerebral circulation is the ICA, within 2 cm of the carotid bifurcation[12]. There are three molecular stages in the natural history of this disease[13]: (1) the fatty streak phase, in which macrophages are transformed into foam cells due to oxidative stress, (2) the formation of a fibrous cap (FC) by myocytes, and (3) the fibrous surface of the so-called complex plaque will rupture, causing ulceration, intraplaque hemorrhage (IPH), *in situ* thrombosis, or calcification. It is during this stage that the disease becomes symptomatic[13]. Furthermore, Glagov et al.[14] described how coronary arteries also change throughout the evolution of plaques. Initially, the artery will enlarge to maintain a proper or normal lumen due to the growing atheroma. With > 40% stenosis, the plaque's area will continuously increase up to the point where it will encircle all the arterial walls. Eventually, the artery will not be able to keep up with its enlargement to preserve patency. This report proposed that the plaque disrupts the widening of the artery because it covers up the endothelium that can react and remodel the vessel in response to the increased flow[14].

The current plaque classification established by the American Heart Association (AHA) comprises six types of lesions with their respective subtypes but does not include the correlation between plaque composition and size with the degree of occlusion[15]. One must remember that these studies pertain to coronary disease and have been extrapolated to ACD.

Symptomatic carotid stenosis

CEA is currently the gold standard for treating ACD, whether symptomatic or asymptomatic, whereas CAS is usually reserved for those with a high cardiovascular risk for surgery[16]. One of the more significant disadvantages of both procedures is the risk of restenosis due to neointimal hyperplasia or recurrent atherosclerotic plaque[17].

Medical treatment

When carotid atherosclerotic stenosis is associated with minor non-cardioembolic IS, such as a National Institutes of Health Stroke Scale < 4 or a high-risk transient ischemic attack (TIA) with $ABCD^2 \geq 4$, dual antiplatelet therapy (DAPT) becomes necessary[18]. This therapy has shown greater long-term results than monotherapy in reducing new heart attacks and death, especially if it is started within the first 7 days after the index event[18]. The first-line pharmacological therapy in these cases is a combination of aspirin and clopidogrel, recommended from 3 weeks to 3 months after infarction, as informed by two large trials[18]. Regarding ticagrelor, its addition (90 mg twice a day) to aspirin may be beneficial with a minor stroke or a high-risk TIA in the context of ipsilateral intracranial stenosis of > 30%, for up to 30 days[18].

Surgical treatment

CEA is a surgical procedure that aims to remove plaque from the carotid artery, reducing the risk of stroke in patients with carotid artery disease.

Some patients may particularly benefit from CEA:

- Older patients with highly calcified vessels
- Contraindications to double antiplatelets
- Those with no previous ipsilateral CEA
- Furthermore, the lesion should be surgically accessible.

In symptomatic patients, the NASCET[6] and the ECST[7] trials demonstrated that CEA is effective in reducing the risk of stroke in selected patients with high-grade (70-99%) carotid stenosis. NASCET found that CEA reduced the risk of ipsilateral stroke from 26% to 9% over 2 years, whereas ECST found a similar reduction in risk from 26% to 13% over 3 years. Both trials concluded that CEA was most beneficial for patients with high-grade stenosis and that the benefits of surgery decreased as the degree of stenosis decreased[6,7]. For patients with a moderate (50-69%) and a life expectancy of at least 3 years, revascularization should be considered if it can be done within 2 weeks from symptom onset, as with high-grade lesions[18].

Endovascular treatment

The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST), which included 2502 patients with symptomatic and asymptomatic carotid stenosis (ACS), was randomly assigned either to an endovascular

or surgical approach. There was no difference between the two groups for the primary outcome (which included death, stroke, and myocardial infarction), with similar results for asymptomatic patients[19].

The following is the current consensus in the American and European guidelines regarding CAS in asymptomatic ACD:

For an endovascular approach in patients with a symptomatic, intracranial ACD and optimal medical treatment, the AHA[18] has no definite answer for using stenting or angioplasty alone to prevent IS. As such, the class of recommendation is 2b (weak) with a level of evidence C (limited data)[18]. Overall, angioplasty and stenting are not recommended as the initial treatment for patients with a stroke or TIA attributable to ACD, except when the patient's anatomy and medical conditions would pose an increased risk for surgery, especially when the stenosis is moderate by non-invasive imaging or > 50% by catheter-based imaging[18].

The 2021 European Stroke Organisation's guidelines[16] make similar recommendations regarding the choice between CEA and CAS, with a preference for the former and the second being relegated to an option after careful consideration and a high risk for the surgical approach.

In addition, these guidelines suggest a risk of in-hospital stroke or death for symptomatic ACD following revascularization to be, ideally, below 4%[16].

ACS

While there is ample data on treating symptomatic carotid stenosis, ACS remains controversial, with advocacy for both an exclusive optimal medical treatment approach and revascularization for certain cases, with increasingly better results for each[20].

At present, the largest trial for intervention in ACS is the Second Asymptomatic Carotid Surgery Trial (ACST-2)[21], which reported that during a 5-year follow-up among 3625 patients, 1% had a procedure-related disabling stroke or death, and 2% had a non-disabling procedural stroke. ACST-2 concluded that serious complications were uncommon for both CEA and CAS, with the latter having a slightly higher incidence of non-disabling procedural stroke, although this difference was non-significant[21]. In addition, stroke risk for ACS was recently assessed in a meta-analysis that found that it was linearly associated with the degree of stenosis, with a greater risk found among those with 70-99% versus those with 50-69% (odds ratio [OR] 2.1), and an even higher risk for those with 80-99% stenosis compared to those with 50-79% (OR 2.5)[22]. It is worth noting that neither of these revascularization trials employed what is now considered to be the optimal medical management[23].

Medical treatment

Management of asymptomatic carotid atherosclerosis disease should be started with low doses of aspirin[24]. DAPT with aspirin/clopidogrel is discouraged as it has not shown greater benefits[25].

A double-blind trial from 2017 reported that the combination of aspirin and rivaroxaban was superior to monotherapy in terms of preventing stroke with better results in the long term, including bleeding risk[25]. In contrast, rivaroxaban monotherapy did not show superior results to aspirin in preventing infarction but was found to increase the risk of bleeding, and thus it is not recommended as monotherapy in carotid atherosclerosis disease[25].

Surgical treatment

The Asymptomatic Carotid Atherosclerosis Study (ACAS)[26] and the first Asymptomatic Carotid Surgery Trial (ACST-1)[27] showed that CEA is beneficial in reducing the risk of stroke in certain populations. ACAS found that CEA reduced the risk of stroke from 11% to 5.1% over 5 years in patients with high-grade (60-99%) carotid stenosis, whereas ACST-1 found a similar reduction in risk from 6.4% to 3.6% over 10 years. However, both trials noted that the absolute benefit of CEA was relatively small and that the risks associated with surgery (such as myocardial infarction, cranial nerve injury, and death) must be carefully weighed against the potential benefits[26,27]. It is worth noting that ACAS was published almost 30 years ago, and ACST-1 followed almost a decade later.

As mentioned before, ACST-2[21], which compared CEA versus CAS in ACS concluded that there was no significant difference in the rates of stroke, myocardial infarction, or death between patients who underwent CEA and those who underwent CAS. However, CEA (4.5%) was found to be slightly more effective than CAS (5.3%) in preventing any type of stroke in 5-year estimates. Overall, CEA is still considered the treatment of choice for patients with ACS[16].

Endovascular treatment

Evidence for the endovascular approach to ACS is scarce. Because of this, most current guidelines

recommend CEA over CAS. Published in 2016, ACT-1 (Randomized Trial of Stent vs. Surgery for ACS) randomly assigned 1452 patients for either carotid stenting or endarterectomy in a 3:1 proportion; there were no differences between groups regarding stroke, myocardial infarction, and death (3.3% for stenting and 2.6% for endarterectomy)[28].

A 2022 meta-analysis[29] published the results of different trials comparing CAE and CAS for ACS (the most recent being ACST-2[21]), concluding that both procedures have similar safety profiles for stroke, death, and myocardial infarction in the long term[29]. Nevertheless, CAS had a higher risk of any stroke during the perioperative period (OR, 1.62 [95% confidence interval (CI), 1.16-2.[24]; p = 0.004, I^2 = 0%) and an increased risk of non-disabling stroke (OR, 1.81 [95% CI, 1.23-2.65]; p = 0.003, I^2 = 0%)[29].

Imaging markers

Doppler ultrasound (DUS)

Carotid DUS is a popular and accessible tool for evaluating carotid plaques, given its widespread availability, ease of use, non-invasive nature, and cost. Still, it is a user-dependent technique, and thus its reliability will vary from center to center. It has a two-dimensional (2D) grayscale mode and a color Doppler mode to detect stenoses.

Color-Doppler US (CDUS) measures velocity on a grayscale image and codes it in color for an enhanced appreciation of blood flow in the segment, which in turn will help detect stenosis[30]. Waveform analysis is one of the three main components of CDUS, along with plaque characterization and grading of the stenosis with Doppler velocity criteria. A pulsed wave Doppler will also measure blood flow velocity which will be shown as a curve for each pulsation, with different morphologies depending on the flow's velocity[30]. Depending on the peak systolic velocity (PSV), each value will be used as a surrogate to determine stenosis percentage.

Severe stenosis will show two waveform changes: *pulsus tardus* (due to delayed upstroke) and *pulsus parvus* (diminished waveform), which in conjunction are usually referred to as *tardus parvus* waveform[31].

Intima-media thickness (IMT)

The 2D mode grayscale –or B-mode– has been used to measure the IMT, which has seen use as a biomarker for early-stage atherosclerosis[31]. IMT should be measured in a segment with no focal lesion[30].

The very definition of an abnormal IMT has not been standardized, with some studies defining it as greater than the 75th percentile, others as > 1 standard deviation from the mean, IMT at the upper quartile, IMT at the upper tercile, or an absolute value of ≥ 0.9 mm or ≥ 1 mm[32]. The American Society of Echocardiography recommends the 75th percentile definition for sex, age, and ethnicity as abnormal[33].

It is uncertain whether effects on IMT progression may reflect a decreased risk of cardiovascular disease (CVD) events. A 2020 meta-analysis by Willeit et al.[34] revealed that for each 10 μm/y reduction of IMT progression, there was a relative risk of 0.91 for CVD (95% CI, 0.87-0.94) and an additional relative risk for CVD of 0.92 (CI 0.87-0.97) achieved independent of IMT progression. It was concluded that the extent of the intervention would affect IMT progression and may be used to predict the degree of CVD risk reduction[34]. On the other hand, a 2007 meta-analysis by Lorenz et al. concluded that each interval increase in IMT over 0.9 mm was associated with a 13-18% higher risk of future stroke and a 10-15% increased risk of myocardial infarction[35]. As it stands, the current ACC/AHA guidelines do not recommend IMT measurement as a marker for risk assessment of a first CVD event (recommendation class III, level of evidence B)[36].

Plaque characterization

Both grayscale and CDUS must be used in conjunction to properly assess the plaque to describe plaque burden, echogenicity, and surface. During plaque screening, the carotid bulb warrants special attention because plaque typically develops earliest in this segment[33].

Echogenicity is described as hypoechoic versus echogenic and heterogeneous versus homogeneous[37]. Hemorrhagic and lipid-rich plaques are more likely to be hypoechoic, a plaque > 50% hypoechogenic is of particular concern, as they have been reported to have an increased likelihood of being symptomatic[38].

Plaque ulceration is another source of emboli, as thrombi are less likely to form on smoothly hyalinized, fibrous, or calcified plaque[37]. CDUS may prove unwieldy or insufficient when trying to characterize the plaque. Ulceration may register as a focal defect, either depression or indentation, or as an anechoic area that extends from within the plaque to the vessel's lumen with no echogenicity in between[31]. The definition of an

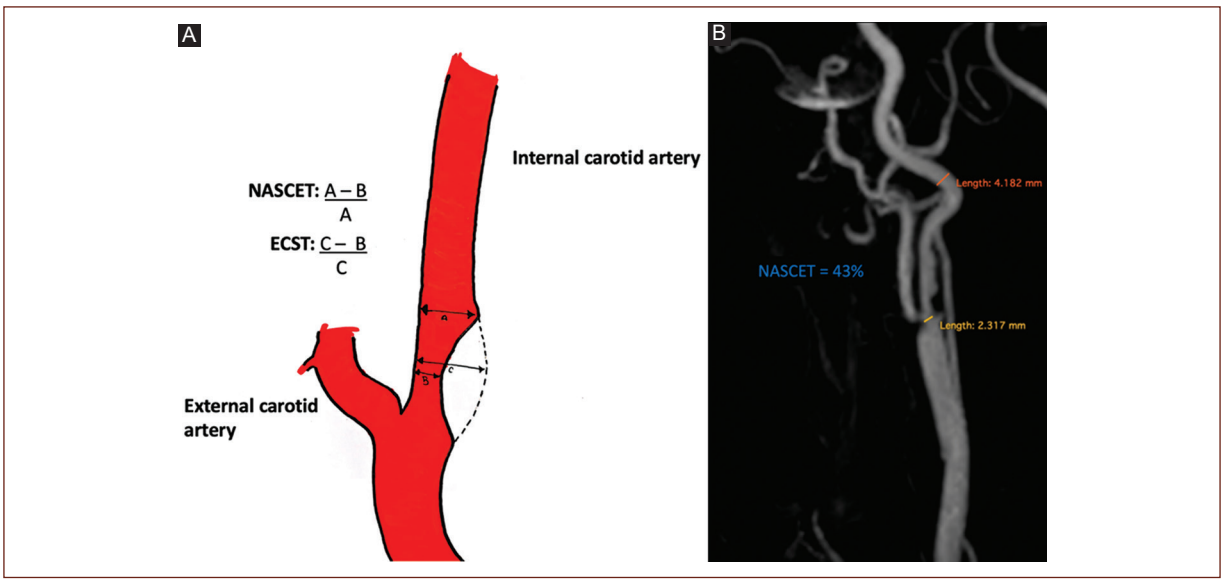

Figure 1. A: NASCET and ECST methods of carotid plaque stenosis. **B:** example of the NASCET method. ECST: European Carotid Stenosis Trial; NASCET: North American Symptomatic Carotid Endarterectomy Trial.

ulcer is a defect > 2 mm in 2 orthogonal planes[37]. All plaques should be assessed in grayscale, Color Doppler, and PSV, as an apparent large plaque with no associated increased velocities warrants further exploration or even new imaging studies.

Estimation of the stenosis

NASCET remains the most popular method to grade stenosis, even if the plaque burden may be underestimated. Spectral Doppler is considered a reliable tool to measure stenosis, with PSV recommended as the primary Doppler criterion for grading ICA stenosis – until the stenosis is > 95%[37], as PSV may register as either normal or even low.

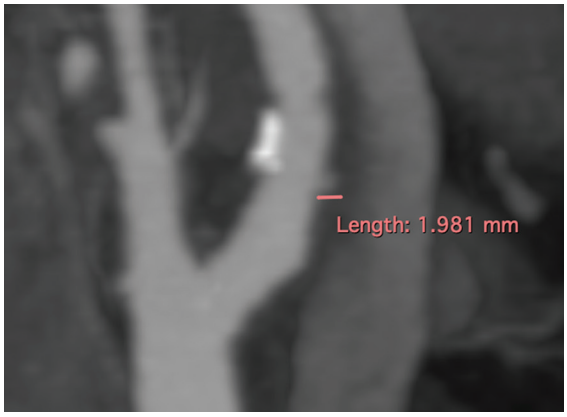

Figure 2. Ulcerated plaque with contrast entering the plaque, labeled with a length of 1.981 mm.

Computerized tomography

Multidetector computerized tomographic angiography (MDCTA) is a valuable tool for the evaluation of ACD. It identifies and classifies stenosis and ulcerated plaque with great accuracy[39]. The different techniques offered by MDCTA include maximum intensity projection, multiplanar reconstruction, shaded surface display, and volume rendering[40].

The degree of stenosis is classified according to the NASCET criteria, in which the measurements are made in a strictly perpendicular manner regarding the carotid axis. The value is calculated by comparing the stenotic segment's diameter with the most normal distal segment[39] (Fig. 1A and an example in Fig. 1B).

The plaque surface's morphology, especially the irregularity assessed with MDCTA, has been identified as an important risk factor for patients with a 30-69% stenosis, with an increased risk of developing symptoms[40].

Promising results with MDCTA have demonstrated the ability to assess plaque composition, compared to histology[39].

The plaque's surface may be classified as smooth, irregular, or ulcerated; an irregular plaque's surface may fluctuate between 0.3 and 0.9 mm, whereas an ulcerated

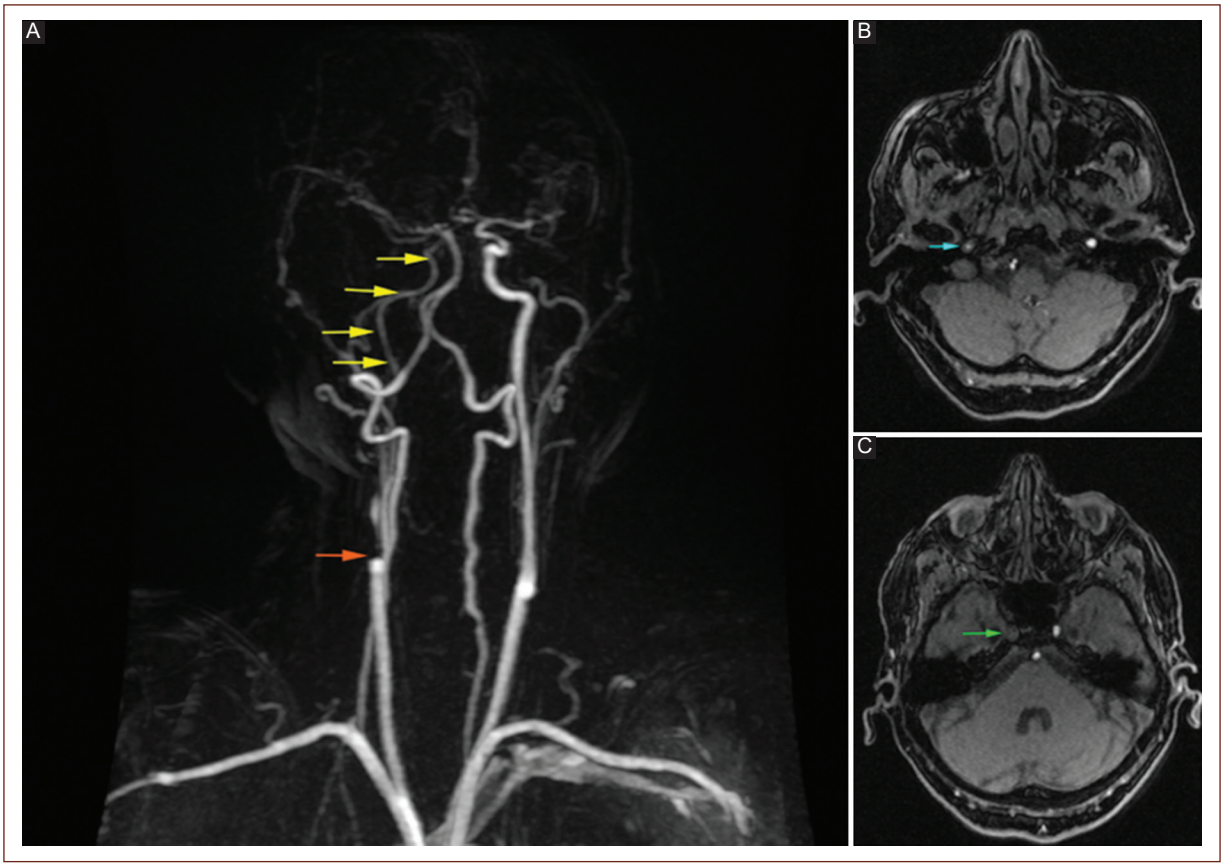

Figure 3. A: 3DTOF of the RICA (yellow arrows) with a decreased signal due to a critical stenosis at the carotid bulb (orange arrow). This image may be confused with hypoplastic vessels, and occlusion in extreme cases. **B:** this may affect distal segments, with a loss of signal of the RICA at the ophthalmic segment (cyan arrow) and **C:** apparent occlusion by the communicating segment (green arrow). 3DTOF: 3D time-of-flight; RICA: right internal carotid artery.

plaque will demonstrate cavities of > 1 mm[8] (Fig. 2). Logically, an irregular surface signals a higher risk for IS, especially when it is an ulceration; nevertheless, such findings may be the evidence of a previous IS, and thus its predictive value is yet not well defined[8].

Magnetic resonance imaging (MRI)

The MRI work-up for a patient with ACD necessitates, at the very minimum, a set of sequences to better identify any findings that might increase the risk for IS: pre- and post-contrast T1-W turbo-spin echo, magnetization-prepared rapid acquisition gradient-echo (MPRAGE), black-blood sequences, fat suppression, and time-of-flight (TOF)[41]. It should be noted that because TOF uses flow to construct a vessel's morphology, slow or turbulent flow may result in loss of signal[42], with an apparent occlusion, and thus should be carefully interpreted; likewise, signal intensity may be different between two vessels because of differences in flow speed, with seemingly hypoplastic or even occluded vessels (Fig. 3). Adding contrast to the study will allow for a better distinction between the FC and the lipid-rich necrotic core (LRNC), whereas black-blood sequences are beneficial to differentiate the lumen from the vessel wall[41]. MRI uses the same criteria as MDCTA for plaque morphology and thickness.

LRNC, FC, and plaque ulceration

LRNC is a compound made up of cholesterol crystals, apoptotic cellular detritus, and calcium particles[8]. Closely linked to the LRNC is the FC: once the cholesterol crystallizes, it will expand, which will also cause the FC to expand and become thinner, with the risk of rupture. These crystals' edges may cut through the neighboring fibrous tissue[43]. A plaque with > 40% of LRNC, along with a thin FC has an increased risk for stroke[8].

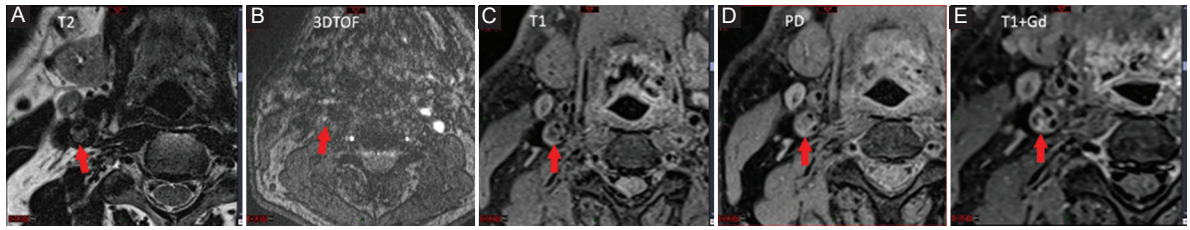

Figure 4. Severe left atherosclerotic carotid disease with a vulnerable plaque assessed with magnetic resonance imaging. Arrows in **A** and **C** point to the lipid-rich necrotic core. Arrow in **B** points to a severely decreased flow due to the stenosis. Arrow in **D** reveals intraplaque hemorrhage. The arrow in **E** shows enhancement after gadolinium. PD is hyperintense compared to T2. 3DTOF: 3D time-of-flight; PD: proton density; Gd: gadolinium.

While both CT and MRI may detect lipidic components, MRI has been found to be superior for the characterization of the LRNC, given that this technique can distinguish between IPH and LRCN (Fig. 4)[44]. Multi-contrast MRI for carotids with T1 and T2-weighted black-blood sequences, as well as the bright-blood TOF, have been histologically validated for detecting LRNC; gadolinium may help with the distinction between LRNC and hyperintense fibrous tissue[41].

The FC's status must be assessed: whether it is intact, thinned, or ruptured, as plaque thickness and integrity are associated with varying degrees of IS risk[41]. Multicontrast MRI (TOF, proton density, T1, and T2, Fig. 4) has proved to be a very useful tool to determine FC integrity[45].

A ruptured FC will expose the plaque's thrombogenic contents for platelets and coagulation factors, which may lead to clot formation and distal embolism[46]. A thin but intact FC will feature a smooth surface and will not enhance after contrast, whereas a ruptured FC will demonstrate an interrupted and hypointense band after contrast[41].

IPH

IPH is one of the key features in identifying an unstable plaque and contributes to the acceleration and growth of the LRNC[8]. A plaque with IPH is considered to be in a more advanced stage than the ones containing only LRNC and FC[41].

IPH may be better appreciated with common MRI sequences[8]. It will be hyperintense in all T1-weighted sequences, including MPRAGE, TOF, and fast spin-echo[41].

IPH has been reported with an adjusted HR of 11.0, independent of stenosis degree and with no difference for sex[47]. Furthermore, it is more prevalent in ipsilateral ICAs to embolic strokes of undetermined source[48], even if other causes are still possible[8].

Conclusion

Revascularization for ACD is an evolving field with an increasing body of evidence for different types of medical and surgical treatments. Treatment for ACS is less certain, although trials like CREST-2[49] are expected to shed light on the possibilities of both CEA and CAS, plus medical management.

Plaque analysis is now paramount to evaluation, as stenosis alone has often proved to be an unreliable marker of stroke risk.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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