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EDITORIAL

Using 3D printing to improve accessibility of the Nine-Hole test in Mexico

Uso de la impresión 3D para mejorar la accesibilidad de la prueba de Nueve Hoyos en México

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The Nine-Hole Peg Test (NHPT) is a test that is used to evaluate manual dexterity and fine motor skills. It was designed by Kellor et al. in 1971 and Mathiowetz et al. in 1985 published detailed instructions for the design and application of the test[1,2]. The main advantages of this test are that it is simple, easy to transport, easy to administer and requires a short time to administer. The NHPT is used to assess manual dexterity in patients with hand injury and in neurodegenerative diseases such as Parkinson's disease[3] or multiple sclerosis[4] in which the NHPT is part of the Multiple Sclerosis Functional Composite which is a standardized test used primarily in clinical studies and consists of three assessments: walk/leg function, arm and hand function, and cognitive function[5].

In our country, access to the NHPT is limited. It is difficult to find the test even in specialized stores. Facing this problem, we undertook the task of designing a 3D model of the NHPT with the use of SketchUp 2018 software that was printed on a Dremel 3D printer model 3D20 (Fig. 1). We can assume that this tool is valid for clinical evaluation as it complies with the measures of the original test design proposed by Mathiowetz et al.

We have performed preliminary measurements in 18 subjects, with a median age of 28 years (interquartile range = 24-66) and no history of neurological diseases, obtaining promising results. Intraclass correlation coefficient (ICC) from dominant hand (Jamar and 3D printed) was 0.769 (95% confidence interval: [CI] 0.388-0.913) and for non-dominant hand was 0.832 (95% CI: 0.543-0.937). ICC estimates and 95% CI were calculated using the Statistical Package for the Social Sciences (SPSS) version 25 (SPSS Inc., Chicago, IL) based on a mean-rating (k = 2),

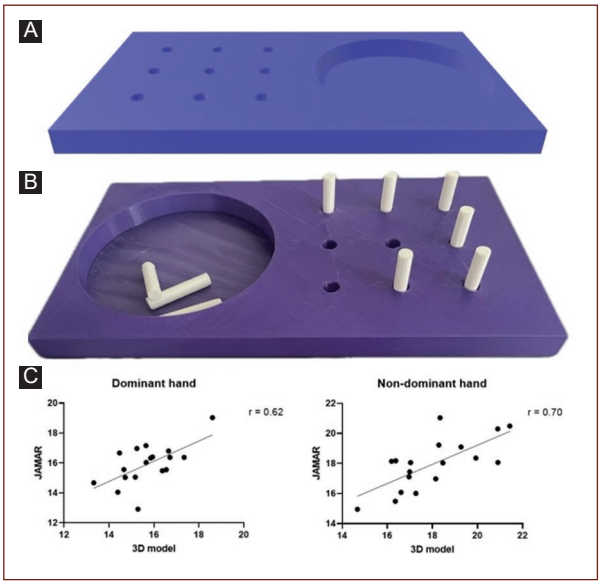

Figure 1. Nine-Hole Peg Test model. **A:** model created with SketchUp 2018. **B:** model printed with Dremel 3D20. **C:** analysis of the correlation between Jamar times and the 3D model.

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absolute-agreement, two-way mixed-effects model. As shown in figure 1, the correlation coefficient for the dominant hand was 0.62 (p = 0.006) while for the non-dominant hand, it was 0.70 (p = 0.001).

It is undeniable that parts printed on a 3D printer can become unspecific. Factors such as printing speed and the height of each layer can influence the final measurements of the model and in the case of the NHPT not present the exact measurements[6]. However, the use of free software such as Cura or commercial software such as Simplify, and the standardization of printing profiles, can help to diminish these effects and help to maintain the proper configuration of the model.

With the advance of technology, tools have been designed and evaluated that allow patients to be evaluated remotely or by virtual reality. However, it has been reported that in a virtual NHPT, patients take longer to perform the test compared to the traditional test[7], so, despite being a viable option, new standards would have to be adapted for the validation of these new tools.

The regular use of the test allows neurologists to perform a comprehensive evaluation of the patient with upper-limb alterations. Since, in our country, the accessibility to this test is limited, we believe that 3D printing can be the way to have valid and low-cost models. The average printing time for this model is in the range of 2.5-5 h, depending on the print settings and the cost of the material required to print this model (standard polylactic acid filament) would be in the range of 5-15 dollars. Several universities in our country have 3D printers and could help to replicate models or even propose new tests that could further improve the clinical neurological evaluation.

The STL files for printing this model will be shared upon request with the corresponding author.

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ORIGINAL ARTICLE

Importance of brain MRI to evaluate immediate intracranial complications after carotid stenting in patients with significant carotid stenosis

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Abstract

Objective: *This prospective study aimed to fill the current knowledge gap in the literature by identifying the demographic and clinical characteristics of patients with carotid stenosis who undergo carotid arterial stenting.* **Methods:** *A cohort of 49 patients who underwent carotid artery stenting (CAS) from January 2021 to August 2022 was analyzed. Demographic information and data related to the existence of adverse neurological events were collected.* **Results:** *Stent placement achieved a 93.8% success rate when measured using the NASCET measurement criteria. Post-CAS neuroimaging revealed multifocal diffusion-weighted imaging (DWI) restriction in 8.16% of patients, hypointensity on susceptibility-weighted imaging in 8.16%, and focal DWI restriction in 32.65%, with no clinically significant deficits observed. A statistically significant association (p = 0.015) between severe stenosis and multifocal neuroimaging events was observed.* **Conclusions:** *Neurological complications observed by neuroimaging after CAS were not an indicator of an increased risk of clinically important adverse events at follow-up.*

Keywords: *Carotid stenosis. Self expandable metallic stents. Magnetic resonance spectroscopy. Radiology. Interventional.*

Importancia de la RM cerebral para evaluar las complicaciones intracraneales inmediatas después de la colocación de un stent carotídeo en pacientes con estenosis carotídea significativa

Resumen

Objetivo: *Este estudio prospectivo tuvo como objetivo llenar el vacío de conocimiento actual en la literatura mediante la identificación de las características demográficas y clínicas de los pacientes con estenosis carotídea que se someten a la colocación de stents arteriales carotídeos.* **Métodos:** *Se analizó una cohorte de 49 pacientes sometidos a stent arterial carotídeo (CAS) entre enero de 2021 y agosto de 2022. Se recogió información demográfica y datos relacionados con la existencia de eventos neurológicos adversos.* **Resultados:** *La colocación del stent alcanzó una tasa de éxito del 93,8% cuando se midió utilizando los criterios de medición NASCET. La neuroimagen posterior al NASCET reveló una restricción multifocal en la imagen ponderada por difusión (DWI) en el 8.16% de los pacientes, hipointensidad en la imagen ponderada por susceptibilidad (SWI) en el 8,16% y restricción focal en la DWI en el 32,65%, sin que se observaran déficits clínicamente*

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significativos. Se observó una asociación estadísticamente significativa (p = 0.015) entre la estenosis grave y los eventos de neuroimagen multifocales. **Conclusiones:** *Las complicaciones neurológicas observadas por neuroimagen después de la EAC no fueron un indicador de un mayor riesgo de eventos adversos clínicamente importantes durante el seguimiento.*

Palabras clave: *Estenosis carotídea. Stent metálico autoexpandible. Espectroscopia por resonancia magnética. Radiología. Intervencionismo.*

Introduction

Ischemic stroke has become a major global health problem, due to its high prevalence and the significant social and economic impact attributed to it. Regarded as a medical emergency, comparable to acute ischemic heart disease, the incidence of stroke within the European population is approximately 186.96 cases/100,000 inhabitants annually. Notably, 87% of these cases are ischemic strokes, with the remaining incidents attributed to cerebral hemorrhages (10%) and subarachnoid hemorrhages (3%)[1].

A primary contributor to ischemic strokes is extracranial carotid artery stenosis (CAS). This condition is characterized by severe atherosclerosis in the carotid arteries, significantly elevating the risk of subsequent strokes[2]. Such stenosis can induce cerebral hypoperfusion, potentially leading to brain atrophy, dementia, or cognitive impairment[3]. To mitigate the risk of further strokes in patients with CAS, carotid revascularization procedures, such as carotid endarterectomy (CEA) and CAS, are employed. CEA, considered the gold standard, is particularly effective in patients with low morbidity and mortality rates < 6% in symptomatic patients and under 3% in asymptomatic individual[4]. In contrast, CAS, noted for its rapid recovery, minimal surgical risks, and continuous neurological monitoring during the procedure, has gained popularity, especially among high-risk patients.

CAS offers several advantages over traditional surgical techniques: a recovery period of merely 24 h, reduced hospital stay, no risk of cranial nerve damage in the neck, and less surgical invasiveness. The patient remains conscious throughout the procedure, allowing for continuous neurological monitoring and observation of carotid blood flow. Due to these benefits, CAS has been widely adopted, particularly in patients with elevated surgical risks.

The study's principal objective is to examine neuroimaging changes in patients with carotid stenosis, both pre- and post-revascularization and to evaluate the impact of new neurological events, as observed through neuroimaging post-procedure, differentiating between asymptomatic and symptomatic cases.

Materials and methods

Study design

Prospective single-center study from November 2021 to May 2022, was approved by the local ethical committee (reference number: C.P.-C.I. PI20/126) and was carried out in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants for both the procedure and the study. The primary outcome was technical success objectively assessed by post-CAS angiography. Secondary outcomes evaluated CAS-related complications by comparing pre- and post-CAS treatment brain magnetic resonance imaging (MRI).

Study population and eligibility

From November 2021 to May 2022, a total of 49 consecutive patients were performed with the intention of CAS. All patients had CAS with or without contralateral stenosis. Stenosis was documented by neck duplex ultrasound, computed tomography angiography, or MR angiography.

Patients were selected according to the following inclusion and exclusion criteria.

Inclusion criteria

Age over 18 years without upper limit, symptomatic stenosis > 50% demonstrated by imaging tests and angiography; or asymptomatic stenosis > 70% and more than one risk factor for future embolism (progressive carotid stenosis) confirmed by Doppler study of the supra-aortic trunks or magnetic resonance angiography, transient ischemic attack, or ischemic stroke occurring in the supply area blood from the ipsilateral carotid artery in the past 6 months and complying with the indications for CAS.

Exclusion criteria

The existence of dementia caused by other reasons (such as Alzheimer's disease), people with problems of

consciousness or confusion without the ability to cooperate, subarachnoid hemorrhage, cerebral hemorrhage or history of intracranial tumor, people with neuropsychiatric diseases, hydrocephalus, claustrophobia or inability to perform a brain MRI.

CAS pretreatment assessment

The pretreatment evaluation included assessment of the degree of stenosis using non-invasive imaging, neurological evaluation (NIH Stroke Scale) performed by a neurologist with more than 15 years of experience in the treatment and follow-up of stroke patients, laboratory results, and a 12-lead electrocardiogram.

Patients received antiplatelet therapy with oral enteric-coated aspirin (100 mg/day) and clopidogrel (75 mg/day) per day at least 3 days before the procedure to reduce periprocedural platelet embolism. Patients using long-term anticoagulation changed their treatment to heparin.

CAS procedure protocol

All CAS procedures were performed by two interventional radiologists with extensive experience in endovascular techniques. The endovascular procedure was performed with local anesthesia at the puncture site and conscious sedation for continuous neurological monitoring of the patient. The technique used in previous studies[5].

Through a femoral approach, selective carotid angiography was performed using a 5F diagnostic catheter (Seldinger technique). Standard anteroposterior and lateral intracranial views were obtained in all cases to establish the adequacy of the intracranial collateral circulation through the external carotid and anterior communicating arteries and to document any intracranial stenotic lesions. The location, length and degree of stenosis, flow compensation through the circle of Willis, and the presence of anastomosis between the internal and external carotid arteries were evaluated. To maintain activated clotting time during the procedure, a bolus of intravenous heparin (5000-7000 IU) was administered.

A 0.035-inch guidewire (Terumo Medical Corporation, USA) was advanced through a spinal microcatheter (5F) to engage the stump of the internal carotid artery internal stenosis. After confirming the tip in the distal true lumen with multiple angiographic projections with Ioversol 320 mg (optiray guerbet) with a flow rate of 12 mL and 4 cc/s. An embolic protection device (EPD) (Emboshield, Abbott Vascular, Santa Clara, CA, USA) was advanced and deployed distally if the anatomical conditions and degree of stenosis permitted. A self-expanding stent (Acculink, Abbott Vascular, Santa Clara, CA, USA) was placed across the stenosis, usually a 6-8 mm × 40 mm cone-shaped stent. Finally, a final intracranial angiogram was obtained to confirm antegrade perfusion and evaluate residual stenosis.

Depending on the operators, the decision was made to postdilate the lesion using balloon angioplasty. The decision was made to predilate in cases where it was impossible to cross the stenosis with the protection system and/or stent system. After stent placement, anteroposterior and lateral cerebral angiograms were obtained to exclude any embolic branch occlusion and document new flow patterns. Technical success was defined as a final residual diameter stenosis < 50% with distal antegrade filling of the middle cerebral and anterior cerebral arteries after the intervention. Residual stenosis was measured using the NASCET measurement criteria.

After the procedure, percutaneous closure devices were used to remove the femoral sheath. All patients were monitored in the neurology unit for 24-48 h after treatment. Antiplatelet agents were administered after the procedure using clopidogrel 75 mg for 4-6 weeks and aspirin 100 mg indefinitely.

The technical success of the CAS stent was defined as the ability to recanalize stenotic carotid lesions and correct deployment of the stent with better cerebral blood flow compared to the subsequent angiographic study.

Pre-CAS and post-CAS brain MRI evaluation

All 49 patients underwent brain MRI (Ingenia S 1.5T; Philips, Germany) with the following weighted sequences: T1, T2, FLAIR, diffusion, and susceptibility-weighted images. Brain MRI and MRI angiography were performed 24 or 48 h before CAS and follow-up MRI imaging 24 h after CAS.

The degree of stenosis was defined as mild (0-50%), moderate (50-70%), and severe (more than 70%) according to the European Carotid Surgery Trial criteria.

Based on the imaging findings observed on post-procedure MRI, patients were classified into the following categories:

– Absence of adverse neurological findings: if the patient does not present new images in the post-procedure brain MRI.

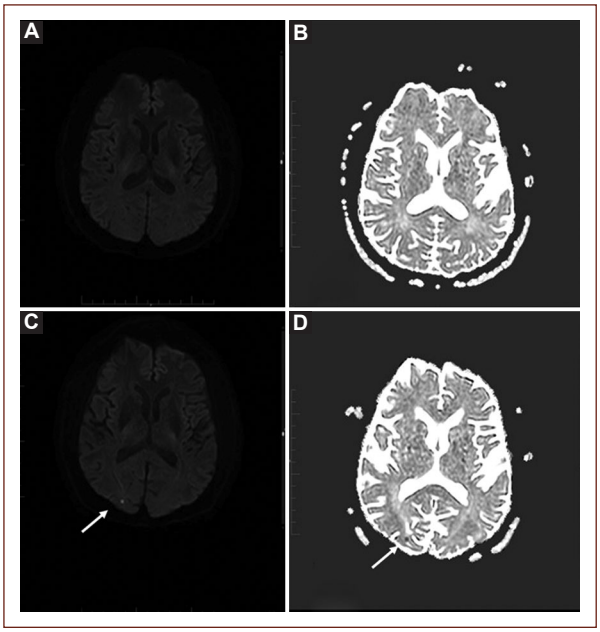

Figure 1. A: magnetic resonance imaging of the brain with diffusion-weighted imaging, and the apparent diffusion coefficient map (**B).** It was conducted 24 h before the placement of the right carotid stent, showing no significant findings. **C** and **D:** a white arrow indicates an area with focal restricted fluid diffusion located in the right occipital hemisphere, performed 24 h after the insertion of the left carotid stent.

Table 1. Demographic data of the study sample

Variable	Patients (n = 49) (%)
Age (years)	71.52 ± 9.52
Sex	
Male	40/49 (81.6)
Risk factors	
Hypertension	42/49 (85.7)
Dyslipidemia	43/49 (87.7)
Diabetes mellitus	25/49 (51)
Smoking	28/49 (57)
Cardiac arrhythmias-atrial fibrillation	15/49 (30.6)
Chronic kidney disease	11/49 (22.4)
Cervical radiation therapy	4/49 (8.16)
Neuroimaging findings 24 h	
No events	25/49 (51)
Focal restriction DWI	16/49 (32.65)
Multifocal restriction DWI	4/49 (8.16)
Hypointensity susceptibility-weighted imaging	4/49 (8.16)
Right or left carotid stenting	
Right internal carotid artery	23/49 (47)
Left internal carotid artery	26/49 (53)
RICA stenosis	
Moderate	3/49 (6.1)
Severe	20/49 (40.8)
LICA stenosis	
Moderate	8/49 (16.3)
Severe	18/49 (36.7)

DWI: diffusion-weighted imaging.

– Focal ischemia: it was defined as small ischemic areas not visualized in the brain MRI before CAS belonging to a single vascular territory (Fig. 1).
– Multifocal ischemia: visualization of ischemic areas not visualized in the brain MRI before CAS belonging to more than one vascular territory (Fig. 2).
– Cerebral microhemorrhage: visualization of hemorrhagic or microhemorrhagic areas not seen on brain MRI before CAS (Fig. 3).

Statistic analysis

To describe the different qualitative variables of the sample, absolute frequencies (n) and relative frequencies expressed in percentages (%) were used. For the quantitative variables, the mean and standard deviation were calculated.

For the inferential analysis and to determine the association between qualitative variables, the Pearson $\chi 2$ test (X2) or the likelihood ratio test was used. By analyzing the association between a qualitative and quantitative variable, the normality of the sample was determined. If the hypothesis of normality was not rejected, parametric tests were used to compare means: Student's t for independent samples in the case of two means and analysis of variance in cases where there were more than two means.

The level of significance (α error) was set in all cases at 0.05 for a confidence level of 95%. All statistical calculations and analyzes were performed with the statistical analysis program IBM Statistical Package for the Social Sciences 22.0 for Windows.

Results

A total of 49 patients with a mean age of 71.52 years (range 50-90) were treated with CAS. Patient demographics, risk factors, and morbidities are listed in (Table 1).

Technical success was achieved in 93.8% (46/49) of intervened carotids. Protective devices were used in 75.5% (37/49) of patients. Post-stent balloon dilation was performed in 93.8% of patients (46/49), with predilation being necessary in 14.2% (7/49).

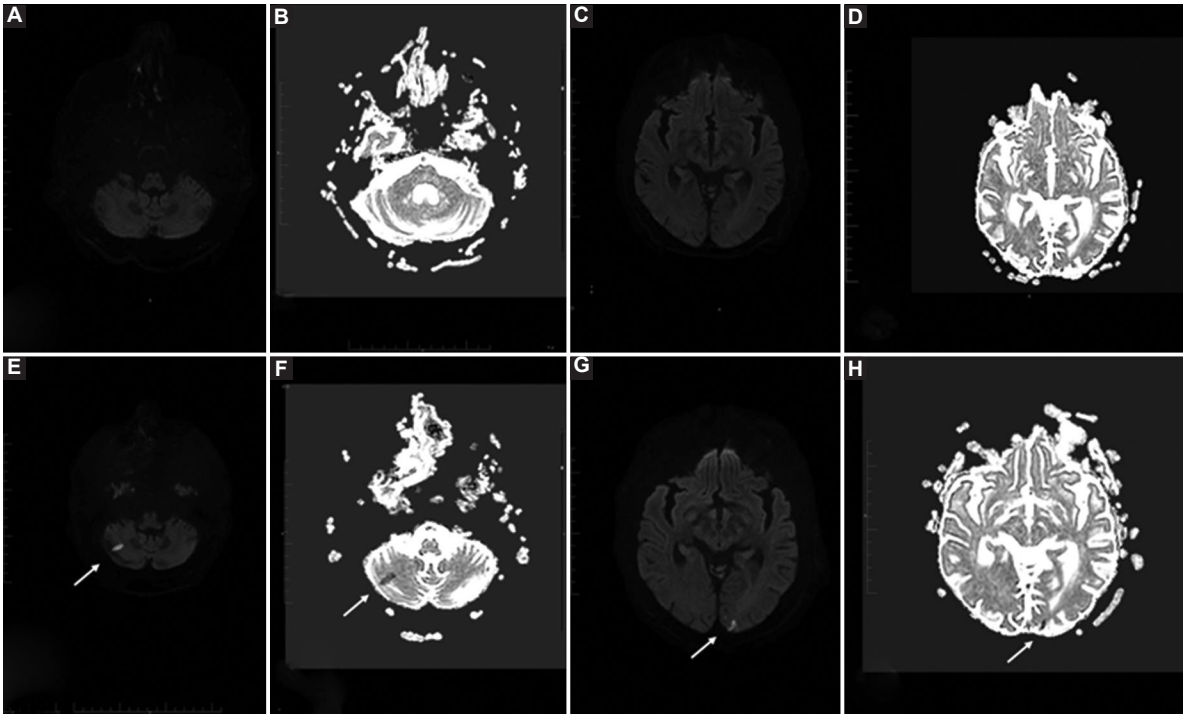

Figure 2. Magnetic resonance imaging of the brain with diffused weighted imaging (**A** and **C**), and apparent diffusion coefficient maps (**B** and **D**), performed 24 h before placement of the left carotid stent. No important findings are seen in the supratentorial and infratentorial. **E-H:** white arrows indicate multifocal areas with restriction of fluid diffusion located in the right cerebellar hemisphere and in the left occipital cortico-subcortical region, performed 24 h after left carotid stenting. No relevant clinical symptoms were observed in this patient.

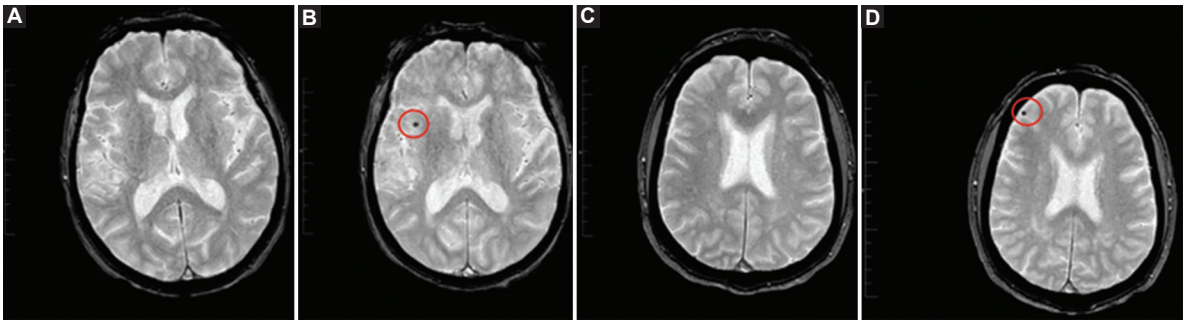

Figure 3. A: brain magnetic resonance imaging study with gradient echo sequence, performed 24 h before insertion of the right carotid stent. No significant findings were seen in the supratentorial sections. **B-D:** a red circle indicates a punctate area, compatible with a focal hypointensity in susceptibility weighted imaging area located in the right hemisphere, performed 24 h after right carotid stenting. No relevant clinical symptoms were observed in this patient.

Regarding the neurological events observed by neuroimaging after CAS, multifocal ischemia occurred in 4/49 patients (8.16%), microbleeds in another 4/49 patients (8.16%), and focal ischemia in 16/49 patients (32.65%), although none of the patients reported a relevant clinical deficit. The degree of stenosis demonstrated a statistically significant correlation ($p = 0.015$) with the appearance of adverse neurological events manifested after CAS in neuroimaging (Table 2), so patients who presented post-procedural ischemia were more likely to

Table 2. Influence of the degree of stenosis and MRI findings

Variable	No MRI findings			Focal restriction DWI			Multifocal restriction DWI			Hypointensity susceptibility-weighted imaging		
	n	%	p	n	%	p	n	%	p	n	%	p
Moderate stenosis (50-70%)	8/13	61.50	0.427$^{\times 2}$	3/13	23.10	0.376$^{\times 2}$	0/13	0%	0.015$^{\times 2}$	2/13	15.30	0.279$^{\times 2}$
Total cases of moderate stenosis	13			13			13			13		
Severe stenosis (> 70%)	17/36	47.20		13/36	36.10		4/36	11.10		2/36	5.50	
Total cases of severe stenosis	36			36			36			36		

MRI: magnetic resonance imaging.

have a high grade of stenosis. All patients who presented multifocal ischemia (n = 4) had a stenosis > 70%.

Middle cerebral artery involvement represented 20.8% of the sample with 10 patients, compared to 79.2% (n = 38) who did not have middle cerebral artery involvement.

The procedure time measured in minutes was an average of 44.33 min with a range between 26 and 89 min.

On the NIHHS scale upon admission, the most frequent values were 0, n = 36 (75%); 1, n = 2 (4.2%); 2, n = 2 (4.2%); 5, n = 2 (4.2%); 9, n = 2 (4.2%); while the predominant results at discharge were values 0, n = 37 (77.1%); 1, n = 6 (12.5%); 2, n = 2 (4.2%), which shows an improvement in the neurological status compared to the values upon the patients' arrival at our center.

A total of 3/49 patients (6.12%) died in this 12-month follow-up period. Of these patients, only 1 case occurred due to a neurological etiology, due to an ipsilateral stroke of the treated carotid artery, more than 30 days after CAS implantation. The rest of the cases were due to other non-neurological causes in relation to the patients' comorbidities. A survival of 94.23% of the sample was demonstrated 1 year after carotid stent implantation.

Discussion

Carotid revascularization is a widely used endovascular procedure for stroke prevention. Some studies have been published to evaluate factors associated with embolization during CAS, either using transcranial Doppler ultrasound or comparing imaging studies before and after stent placement. In all of them, the risks of the procedure are associated with comorbidities, unfavorable anatomy, and the characteristics of the injury[6,7]. In a study of 728 patients published by Bijuklic et al.[8], the rate of new brain lesions was analyzed in patients with carotid stenosis, undergoing CAS with EPD, using diffusion MRI, as in our study. The frequency of new ipsilateral ischemic lesions was 33% (241/728), associated with advanced age and HBP, and only 5% (37/72) of patients who showed an alteration in diffusion MRI developed clinical neurological deficits.

In the current study, the results of ischemic complications were somewhat higher, being 40.81% (20/49), including within this percentage small focal and multifocal ischemias in white matter, clinically irrelevant. The complications evidenced by microhemorrhagic neuroimaging were along the same lines somewhat higher, being 8.16% (4/49), compared to the study by Bijuklic et al. (5.8%)[8], although none of our patients reported a relevant clinical deficit.

The only factors that influenced the appearance of post-procedural complications were cardiac arrhythmias and the presence of dyslipidemia (Table 3). The most plausible explanation is that these patients have a higher risk of stroke, since the possibility of releasing thrombi of atheromatous plaque, with the consequent embolic phenomenon, is higher than in patients without these risk factors.

Table 3. Influence of different clinical risk factors on the presentation of adverse neurological events

Variable	No magnetic resonance imaging findings				Focal restriction DWI				Multifocal restriction DWI				Hypointensity susceptibility-weighted imaging			
	N/Y	n	%	p^{RV}	N/Y	n	%	p^{RV}	N/Y	n	%	p^{RV}	N/Y	n	%	p^{RV}
Hypertension	No	4	57.1	0.606	No	2	28.6	0.892	No	1	14.3	0.482	No	0	0	0.412
	Yes	21	46.7		Yes	14	31.1		Yes	3	6.7		Yes	4	8.9	
Dyslipidemia	No	1	14.3	0.054	No	3	42.9	0.074	No	0	0	0.074	No	2	28.6	0.026
	Yes	24	53.3		Yes	13	28.9		Yes	4	8.9		Yes	2	4.4	
Diabetes mellitus	No	14	56	0.271	No	7	28	0.677	No	1	4	0.336	No	2	8	0.936
	Yes	11	40.7		Yes	9	33.3		Yes	3	11.1		Yes	2	7.4	
Smoking	No	9	39.1	0.250	No	8	34.8	0.577	No	2	8.7	0.809	No	2	8.7	0.809
	Yes	16	55.2		Yes	8	27.6		Yes	2	6.9		Yes	2	6.9	
Cardiac arrhythmias	No	20	54.1	0.175	No	10	27	0.358	No	0	0	0.001	No	4	10.8	0.007
	Yes	5	33.3		Yes	6	40		Yes	4	26.7		Yes	0	0	
Chronic kidney disease	No	18	45	0.417	No	13	32.5	0.622	No	4	10	0.254	No	3	7.5	0.924
	Yes	7	58.3		Yes	3	25		Yes	0	0		Yes	1	8.3	
Cervical radiation therapy	No	23	47.9	0.936	No	14	29.2	0.386	No	4	8.3	0.548	No	4	8.3	0.548
	Yes	2	50		Yes	2	50		Yes	0	0		Yes	0	0	

DWI: diffusion-weighted imaging.

73.1% of the patients in our study had a stenosis > 70%. In the majority of cases in which some metabolic or non-metabolic risk factor was present, there was a stenosis > 70%, highlighting its presence in 71.1% of patients with HTN and 75.9% of patients with a habit. Smoking, these findings can be considered a risk factor for carotid stenosis, although like the other risk factors they did not show a statistical association with the degree of stenosis.

Regarding the analysis that related the degree of stenosis and the presentation of new adverse neurological events observed by neuroimaging after revascularization with CAS, ischemia had statistically significant results, so we can affirm that patients who presented ischemia after the procedure had more probability of having high-grade stenosis > 70%. In fact, all patients targeted for new-onset ischemia after CAS had > 70% stenosis, although the number of patients was small (n = 4).

In the present study, neuroimaging neurological complications after CAS were not an indicator of an increased risk of clinically important adverse events at follow-up. The same happened with other well-known risk factors such as diabetes, smoking, or hypertension.

Conclusion

This study reveals that neurological complications objectified by neuroimaging after CAS were not an indicator of a higher risk of clinically important adverse events in the follow-up. The same happened with other risk factors well known such as diabetes, smoking, or hypertension. MRI may overestimate neuroimaging findings following CAS that might ostensibly indicate ischemic or hemorrhagic pathology; however, fortunately, in our study, these findings were not clinically relevant.

Funding

The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical responsibilities

Protection of people and animals. The authors declare that no experiments have been carried out on humans or animals for this research.

Data confidentiality. The authors declare that they have followed their workplace's protocols regarding the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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REVIEW ARTICLE

Cerebrovascular disease as a neurological complication of cardiac myxoma: a case series and review of the literature

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Abstract

Cardiac myxomas are the most common benign neoplasm of the heart, although their prevalence in the general population is relatively low. They are most frequently located in the left atrium and primarily affect women. Although they represent only 1% of cases of stroke, patients with cardiac myxoma are at higher risk of experiencing them. Immediate surgical resection is the treatment of choice to prevent complications. The American Heart Association considers thrombolysis as the most appropriate treatment for stroke in these patients, in addition to thrombectomy as an equally safe treatment. Stroke is among the most common neurological complications, while aneurysms and brain metastases occur less frequently. The objective of this article is to perform a general review of cardiac myxomas, their diagnosis, and secondary neurological complications, in addition to presenting a series of cases reported in a tertiary center in Mexico City. Timely diagnosis and treatment are essential to prevent complications that may jeopardize the patient's life or impair their functionality.

Keywords: *Heart neoplasms. Myxoma. Stroke. Cerebrovascular disease. Brain neoplasms.*

Enfermedad vascular cerebral como complicación neurológica del mixoma cardíaco: serie de casos y revisión de la literatura

Resumen

Los mixomas cardíacos son la neoplasia benigna más común del corazón, aunque su prevalencia en la población general es relativamente baja. Se ubican con mayor frecuencia en la aurícula izquierda y afectan principalmente a las mujeres. Aunque representan solo el 1% de los casos de accidente cerebrovascular, los pacientes con mixoma cardíaco tienen un mayor riesgo de experimentarlos. La resección quirúrgica inmediata es el tratamiento de elección para prevenir complicaciones. La American Heart Association considera que la trombólisis es el tratamiento más apropiado para el infarto cerebral en estos pacientes, además de la trombectomía como un tratamiento igualmente seguro. Entre las complicaciones neurológicas más comunes se encuentran los infartos cerebrales, además de los aneurismas y las metástasis cerebrales con menor frecuencia. El objetivo de este artículo es realizar una revisión general de los mixomas cardiacos, su diagnóstico y las complicaciones neurológicas secundarias, además de presentar una serie de casos reportados en un centro de tercer nivel en la Ciudad de México. El diagnóstico y tratamiento oportunos son esenciales para prevenir complicaciones que puedan poner en peligro la vida del paciente o afectar su funcionalidad.

Palabras clave: *Neoplasias cardíacas. Mixoma. Accidente cerebrovascular. Trastornos cerebrovasculares. Neoplasias encefálicas.*

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Introduction

Cardiac myxomas are the most common benign primary neoplasm of the heart. They have the potential to embolize and grow at the site of implantation, which can cause infarction in other organs such as the brain[1]. It is crucial to perform a timely diagnosis and treatment to prevent complications that endanger life and affect functionality[2].

The aim of this article is to conduct a comprehensive review of cardiac myxomas and their relationship with neurological complications and to present a series of reported cases in a third-level center in Mexico City.

Epidemiology

Cardiac tumors are extremely rare, their prevalence is higher in Europe and North America, with 0.117 and 0.114 cases, respectively, and lower in Turkey and South America, with 0.0413 and 0.058 cases, respectively[2]. The incidence of these tumors is 1.38-30 cases per 100,000 inhabitants/year[3]. Of the total primary cardiac tumors, 80-85% are benign. Among them, 70% are myxomas, 15-20% are lipomas, and 10-15% are papillary fibroelastomas, which are the most common. The remaining 10-20% of primary tumors are malignant[1,4,5].

The prevalence of cardiac myxoma is 0.03% in the general population and the annual incidence is 0.5-1 case/million. Epidemiologically, they are divided into sporadic or familial cases (corresponding to the Carney complex), with the former being the most common, accounting for 95% of myxoma cases[6]. These conditions can occur at any age, with preference for females, with a ratio of 3:1[6,7].

Anatomy

Myxomas have a preference for the atrium as the most common location for growth, although they can affect any cavity of the heart. The affected sites include 60-90% in the left atrium, 12.7 to 28% in the right atrium, 1.7 to 8% in the right ventricle, 0.6-4% in the left ventricle, and 0.8-1.6% are multifocal[4]. Commonly, they originate in the limbus of the oval fossa of the atrial septum. However, they can also arise from the posterior atrial wall, the anterior atrial wall, and the atrial appendage[6].

Myxoma can appear as polyps in up to two-thirds of cases while having a solid or papillary structure in one-third of cases. Compared to papillary myxomas, they are softer. The polyps are pedunculated, more compact, and less prone to fragmentation and subsequent embolization. On the other hand, papillary or villous myxomas are gelatinous, more fragile, and less compact. They have a higher potential for fragmentation and embolization toward the central nervous system, kidney, spleen, limbs, and coronary vessels[6,8].

Histology

Cardiac myxomas consist of spindle-shaped and polygonal star-shaped cells embedded in an amorphous myxoid stroma. Multinucleated cells may also be present in some cases. These cells are arranged in chains or clusters around the capillaries[9]. The tumor surface is often covered by flattened endothelium, while the tumor mass is abundantly supplied with vessels that have thin walls and lack pericytes[10].

The histogenesis of the myxoma is not well understood, but the current understanding is that it originates from primitive pluripotent mesenchymal cells. The genes encoding cardiac precursor markers can reactivate and express themselves in cells of the cardiac myxoma, causing differentiation along endothelial or endocardial lines[11]. A previous hypothesis was that myxomas originated from Prichard structures. These structures are microscopic, lined by thick endothelial cells, and are found in the oval fossa. Another hypothesis suggested that myxomas originated from neuroendocrine tissue[12].

Clinical presentation

The clinical manifestations of myxoma can be divided into three groups. The first is the systemic group, which includes constitutional symptoms such as fever, arthralgia, weight loss, and fatigue. The second group is the cardiac group, caused by the mass effect that interferes with cardiac function and blood flow. This can lead to arrhythmias, regurgitation, or pericardial effusion, with or without tamponade, also affecting the cardiac valves and causing dyspnea, chest discomfort, and syncope. Finally, the third group is the group of embolic complications, which can include pulmonary or systemic thromboembolism caused by the tumor[1].

Neurological complications occur as a result of embolic events. These complications can manifest in various ways, such as neurological syncope, headache, dizziness, seizures, transient ischemic attacks, ischemic or hemorrhagic strokes caused by aneurysm rupture, and brain metastases[13,14]. These complications can initially occur in up to 80% of myxoma cases[13].

Diagnosis

The diagnostic protocol for cardiac myxomas includes imaging studies such as echocardiography, computed tomography (CT), and cardiovascular magnetic resonance (CMR). Less commonly used tests, such as positron emission tomography (PET) and angiography, may also be employed. Each of these studies offers specific information that is valuable for the diagnostic approach, preoperative planning, assessing the disease's extent, and establishing a definitive histopathological diagnosis.

Echocardiography

Echocardiography is the primary diagnostic study and is performed using two modalities: transesophageal echocardiogram (TEE) and transthoracic echocardiogram (TTE). TEE demonstrates superior sensitivity at 100%, compared to 95% for TTE. It also has a higher capability to identify insertion points, with 95.2% compared to 64.5% for TTE. Furthermore, TEE offers advantages in observing small lesions[15].

Echocardiography enables the characterization of tumors based on their size, morphology, location, extent, and hemodynamic effects, as well as the shape of the mass (Fig. 1). Myxomas appear as spherical masses attached to the endocardial surface, sometimes with hypoechoic internal areas, speckled echogenic spots, and typically echogenic calcifications[6,15].

In addition, it enables the assessment of myocardial perfusion and the comparative perfusion of a cardiac mass, enhances the clarity of intracavitary structures, and evaluates vascularization distinguishing between vascular and non-vascular tumors or thrombi relies on how cardiac masses differ in perfusion. Myxomas often have poor blood irrigation, with quantitatively lower perfusion than the surrounding myocardium. Thrombi are avascular and do not perfuse in the echocardiogram, while malignant tumors are highly vascularized due to abnormal neovascularization, resulting in greater enhancement compared to adjacent myocardium[1,7].

In a study involving 27 patients with cardiac myxoma, TTE revealed several findings. Liquefaction was observed in 18.5% (5/27) of the cases, characterized by an irregular anechoic cystic mass with a small fraction of hypoechoic basement. Calcifications were found in 70.4% (19/27) of the cases, presenting a hyperechoic appearance with shadow, multiple nodules in different positions of the heart in 11.1% (3/27), and high proliferative activity was observed in 7.4% (2/27) with irregular masses of large size and wide base, accompanied by abundant blood supply. These echocardiographic characteristics resemble those of malignant carcinoma, and a predilection for the right ventricle is noted[16].

CT

CT is a diagnostic method that can be used as an alternative to echocardiography and CMR. It offers high spatial and temporal resolution, the ability to reconstruct multiplanar images, and rapid acquisition times. These features enable precise delineation of lesion margins and their relationship with tissue planes, which are valuable for surgical planning[1,6].

Myxomas can be observed with CT scans as rounded, movable, lobulated, and well-defined masses, typically with a narrow pedicle. They often have a heterogeneous appearance and may contain areas of calcification. CT is a valuable tool for assessing the size, shape, location, and calcification of myxomas. The appearance of myxomas can vary depending on their composition, such as the presence of hemorrhage, calcification, necrosis, fibrosis, or cystic changes[17]. CT is also useful in tumor staging, as it can detect metastases in cases of suspected malignancy. However, it has some disadvantages, such as radiation exposure and limited temporal and soft tissue resolution when compared to MRI[15].

In non-contrast CT scans, the tumor typically has lower attenuation compared to non-opacified blood. Myxomas often exhibit heterogeneity due to various factors such as hemorrhage, calcification, ossification, necrosis, cysts, or fibrosis. Tumors may also demonstrate visible enhancement after the administration of contrast, although this may be less pronounced than in magnetic resonance imaging (MRI) and could be challenging to observe due to the presence of highly contrasted surrounding blood. Dual-energy CT with a medium iodine concentration is effective in accurately determining if a mass exhibits visible growth[15,17].

CMR

It provides a comprehensive and non-invasive evaluation of the mass, its potential involvement of the cardiac chambers, the pericardium, extracardiac structures, and its surrounding anatomy. This is useful in surgical planning[6]. CMR enables the evaluation of various characteristics of the heart, including morphology, dimensions, location, extent, homogeneity, and the presence of infiltration in the surrounding tissues. In addition, CMR can provide valuable information about

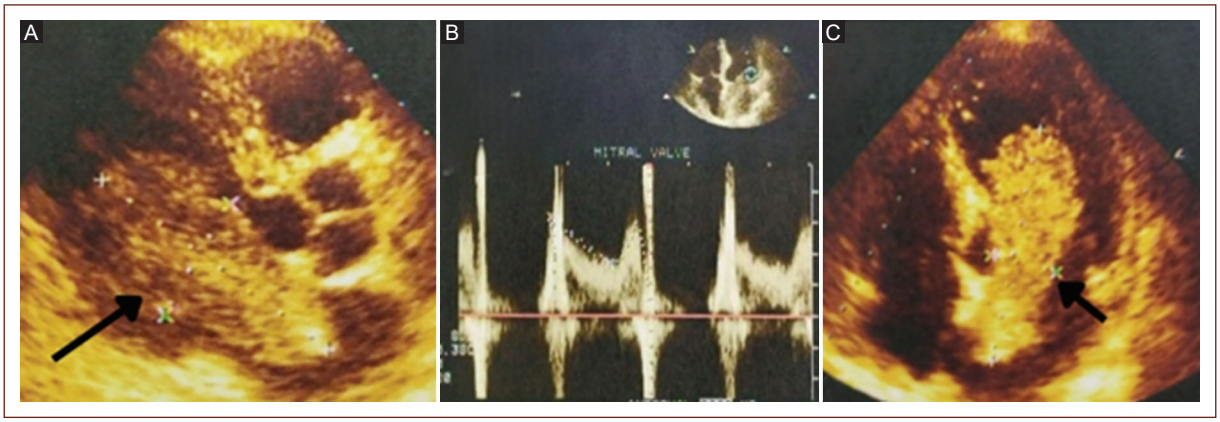

Figure 1. Transthoracic echocardiogram. Two-dimensional echocardiography, parasternal long axis view. **A:** an intracardiac mass is observed, compatible with intracardiac myxoma measuring 74 × 24 mm, with an implantation base at the level of the oval fossa, which protrudes into the ventricular cavity. Apical four-chamber view. **B:** transmitral flow is shown in pulsed Doppler mode, with a mean transmitral gradient of 3.5 mmHg, without valvular obstruction. **C:** an intracardiac mass is observed in the left atrium that protrudes into the ventricular cavity.

signal characteristics that assist in histopathological characterization, such as fatty infiltration, necrosis, hemorrhage, calcification, and vascularity[1,3].

To differentiate between tumors and thrombi, especially if they originate in the left atrial appendage, late gadolinium enhancement sequences performed 10-15 min after contrast administration is useful. Enhancement is usually heterogeneous, and it has been observed that enhanced areas correspond to regions rich in myxomatous tissue and focal inflammation. Internal cysts or necrosis could cause non-enhanced areas as well. First-pass perfusion studies may show mild, heterogeneous enhancement. Another sequence that can help differentiate between myxoma and thrombus is the inversion time. Steady-state free precession cine images are useful for evaluating myxoma function, as mobile lesions can prolapse through the AV valve during diastole. If there is associated mitral valve obstruction, features such as left atrial enlargement, pulmonary venous hypertension with pulmonary vascular redistribution, and pulmonary edema can be observed on X-rays, CT, and MRI[6,15].

Some limitations of CMR are its lower temporal resolution, prolonged acquisition times (30 min-1 h), limited availability, and contraindications in hemodynamically unstable patients or those with older generation cardiac devices, as well as in patients with claustrophobia[15].

PET

PET provides an accurate assessment of the metabolic activity of tumors using fluorodeoxyglucose (18F-FDG). It is useful in the staging of malignant tumors, the detection of possible involvement of the myocardium and pericardium, the evaluation of early responses to cancer therapies, the planning of radiation therapy, and the optimization of sites for biopsy sampling[6,15].

The level of FDG uptake in tumors is a valuable tool for distinguishing between benign and malignant tumors. A study on the detection of benign versus malignant cardiac masses found that this method has a sensitivity of 100% and a specificity of 92%[18].

Angiocardiography

Angiocardiography is rarely used as a diagnostic method due to the availability of non-invasive studies and greater accessibility to other tests such as echocardiography, in addition to the risk of embolization of tumor fragments during the procedure. In angiocardiography, tumors usually appear as filling defects. In cases of left atrial myxoma, a radiotransparent mass within the left atrium can be visualized on the pulmonary angiogram[6,19]. The usefulness of this lies in providing valuable pre-operative information by identifying the blood vessels that supply blood to the cardiac myxoma[19].

Histopathology

In general, immunohistochemistry is used to detect cardiac myxomas. This technique utilizes a variety of biomarkers such as CD31, CD34, CD56, FVII Ag, S-100 protein, calretinin, vimentin, desmin, smooth muscle myosin, α1-antitrypsin, and alpha 1-antichymotrypsin[20].

Myxoma surgery

Functionally, myxomas are considered malignant due to the embolic phenomena they can cause due to the mass effect[6]. To prevent complications, it is important to perform surgical resection as soon as possible. During the procedure, systemic anticoagulation is required for the resection of the myxoma. However, this can increase the risk of intracranial hemorrhage. Despite this risk, various studies and reported series have shown that the procedure is generally safe with low or no mortality[21].

Surgical resection of the myxoma is the preferred treatment to alleviate symptoms and prevent neurological complications. However, there is still uncertainty regarding the best timing for surgery following the occurrence of neurological complications, such as cerebral infarction[6].

At present, there are new surgical approaches and minimally invasive techniques[22], as well as technology used in surgeries such as robotic surgery[23], which helps reduce post-operative complications, further decrease mortality, and restore quality of life early on, in addition to enabling early return to work and daily activities[6]. It has also improved the availability and types of treatments, with reports of up to 2.45% of patients undergoing resection of cardiac myxoma undergoing heart transplantation[2].

The recurrence rate in the resection of benign atrial tumors is lower compared to malignant tumors from the same site (0.8% vs. 22.2%)[24]. Some factors that increase the risk of recurrence include incomplete tumor resection due to limited tumor exposure, multifocal, and genetic conditions[13,22].

Up to 25.5% of patients may experience postoperative complications. These can include pulmonary infections in 5.1% of cases; arrhythmias in 2.3%; embolism in 1.5%; and less frequently, pulmonary hemorrhage, and cerebral hemorrhage secondary to embolism, as well as nerve injuries[25]. In another series, a frequency of 20.6% of arrhythmias during the immediate post-operative period and transient ischemic attacks in 6.7-10.5% was described[26]. The main causes of death in the post-surgical follow-up are heart failure, massive cerebral embolism, and pneumonia[25].

Neurologic complications

Cerebrovascular disease

Embolism can lead to the development of ischemic cerebral infarctions (Fig. 2). In patients with myxoma, systemic embolism occurs in 30-50% of cases, with 50% of those embolizations affecting the central nervous system and the retinal artery. This is attributed to the biological ability of myxoma to detach and cause embolization or to the tumor's morphology, especially when it has an external velvety appearance, which independently increases the risk of embolism (OR = 8.7; 95% confidence interval [CI]: 2.4-42.1; $p < 0.001$)[9].

The risk factors associated with embolism in patients with myxoma include NYHA class I/II heart failure (OR = 2.98, 95% CI = 1.66-5.33, $p < 0.01$), hypertension (OR = 1.41, 95% CI = 1.04-1.92, $p = 0.03$), irregular tumor surface (OR = 3.99, 95% CI = 3.04-5.25, $p < 0.01$), atypical location (OR = 1.81, 95% CI = 1.13-2.88, $p = 0.01$), narrow-based tumors (MD = –0.36, 95% CI = –0.51-–0.22, $p < 0.01$), and increased levels of fibrinogen (MD = 0.62, 95% CI = 0.28-0.95, $p < 0.01$)[27].

Myxomas are a rare cause of ischemic brain infarctions, accounting for < 1% of cases. Cardiac myxomas represent < 1% of cases of stroke. Risk factors associated with a higher risk of stroke include tumor size smaller than 30 mm (OR = 2.652, 95% CI: 1.061-6.627, $p = 0.037$), highly mobile tumors (OR = 2.700, 95% CI: 1.357-5.371, $p = 0.005$), thrombus on the tumor surface (OR = 1.856, 95% CI: 1.003-3.434, $p = 0.049$), and lower levels of BNP (OR = 0.995, 95% CI: 0.989-0.999, $p = 0.047$)[25].

The American Heart Association, in conjunction with the American Stroke Association, considers thrombolysis as a viable treatment for patients with cardiac myxoma presenting with stroke[28]. This statement is based on reported cases that have demonstrated the effectiveness and safety of intravenous and intra-arterial thrombolysis treatment. Clinical improvement, defined by a reduction of 4 or more points on the NIHSS scale, has been observed in 52.2%-64.3% of multicenter series. It has also been found that standard-dose alteplase leads to a higher rate of neurological improvement compared to low doses (64.3% vs. 37.5%, respectively)[29]. In cases where proximal arterial occlusion is documented, mechanical thrombectomy is indicated[30].

Resection of the myxoma prevents neurological complications and should be performed as soon as possible. In patients with cerebral infarction, it has been observed that a prolonged interval between cerebral infarction and myxoma resection is significantly associated with recurrent cerebral infarction ($p = 0.021$)[13], as well as prolonged symptoms at the time of surgery (OR = 1.046, 95% CI: 1.005-1.088, $p = 0.029$)[25].

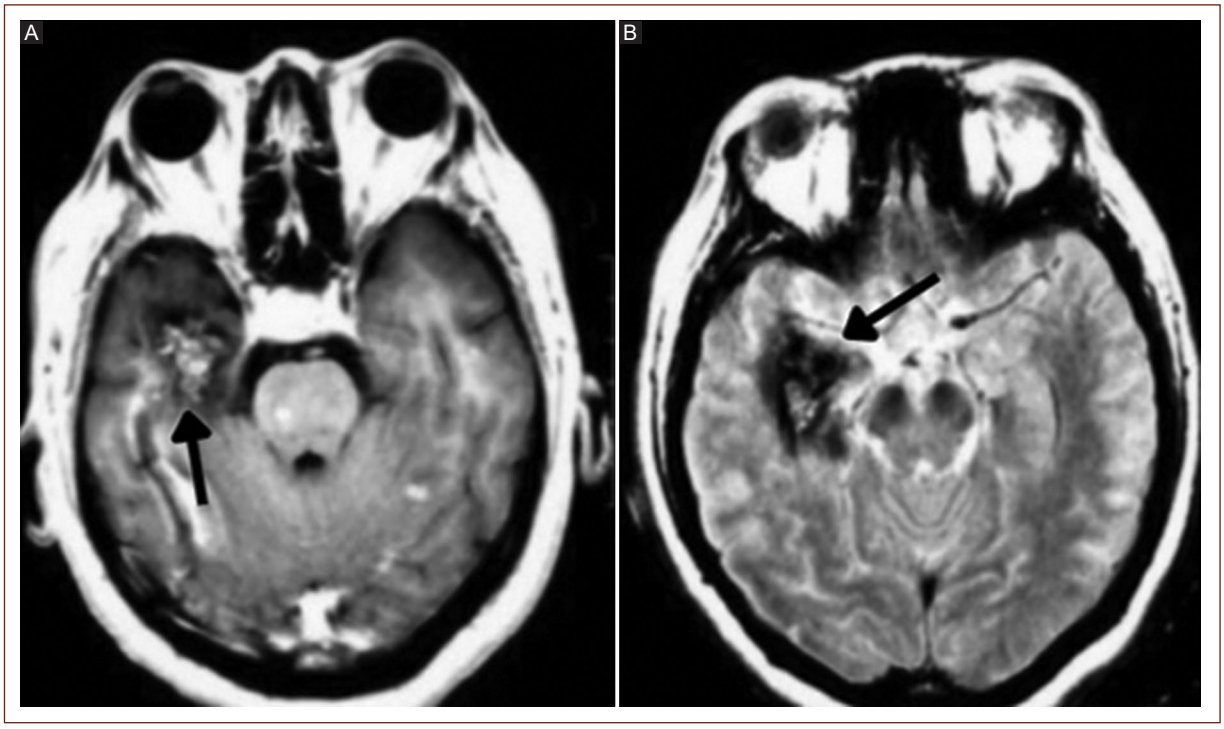

Figure 2. Cerebral magnetic resonance imaging. **A** and **B:** cerebral metastases are shown in the right temporal lobe.

Cerebral aneurysm

Neoplastic cerebral aneurysms are extremely rare but have high morbidity and mortality. The first aneurysm secondary to cardiac myxoma was reported in 1966[31]. They occur in 13-56% of patients with myxoma, with a higher risk of aneurysm rupture (20-25%) compared to aneurysms of other etiologies[32], which can result in intracerebral hemorrhage in 19.6% of cases. Typically, they are treated with open surgery, chemotherapy, radiation therapy, endovascular occlusion with coils, or conservatively[33].

The prognosis of a neoplastic cerebral aneurysm depends on the histology of the primary tumor[34]. It is significantly better in the case of cardiac myxomas compared to choriocarcinoma or other carcinomas ($p < 0.0001$). The mortality rate for cardiac myxomas is 11.4%, while for choriocarcinoma and other carcinomas, it ranges from 60.9% to 92.3%, respectively. Furthermore, 77.3% of patients with cardiac myxomas remain stable, either with or without the disappearance of the aneurysm[35].

At present, there are no established guidelines for the treatment of aneurysms caused by cardiac myxomas. However, a conservative approach and regular radiological monitoring are typically preferred. In most cases, the aneurysms remain stable, and in some instances, they may even regress spontaneously. It has been observed that the risk of delayed cerebral aneurysm formation is not reduced, even if a cardiac tumor resection is performed[36].

Brain metastases

Brain parenchymal metastases are typically removed through surgical resection[35]. Studies have shown that the combination of temozolomide and radiosurgery can help eliminate and control the recurrence of metastatic myxoma[14]. In addition, it has been reported that low-dose radiation combined with chemotherapy can assist in the degradation of metastases. An alternative option is frameless stereotactic radiosurgery, which is less invasive compared to endovascular or open surgery and has fewer systemic effects from chemotherapy[36].

Prognosis and surveillance

Benign primary neoplasms of the heart have a late mortality rate of 0.79%[2]. Among a series of 180 surgically treated patients, the mortality rate was 2.4% and the tumor recurrence rate was 0.8% during an average follow-up period of 48 months[24].

Cardiac myxomas have a disease recurrence rate of 2-3%[37] and neurological complications in up to 12% of

Table 1. Summary of characteristics of patients with myxoma and cerebrovascular disease

Patient	Age/Gender	Antecedent	Location	Clinical presentation	Affected arterial territory	Myxoma treatment	Treatment	mRS at egress	mRS at 6-month follow-up
1	51/M	Dyslipidemia and alcoholism	Left atrial myxoma	Dysarthrias, left central facial paresis, left hemiparesis NIHSS 4	Right middle cerebral artery	Myxoma resection surgery	Thrombolysis	1	1
2	37/M	Dyslipidemia	Left atrial myxoma	Loss of awake state, motor aphasia, right hemiparesis, initial NIHSS 4	Left middle cerebral artery	Myxoma resection surgery and mitral valve plasty	Thrombolysis	2	2
3	44/F	Acute arterial insufficiency and supracondylar amputation	Left atrial myxoma 36mm × 18 mm	Loss of awake state, seizures, initial NIHSS 10	Left middle cerebral artery	Myxoma resection surgery	Thrombectomy	3	3
4	54/F	Dyslipidemia	Left atrial myxoma	Right-hand paresis, dizziness, and decreased visual acuity	Multiple territories	Myxoma resection surgery and mitral valve plasty	ASA, statins	4	4
5	39/M	Diabetes mellitus type 2, dyslipidemia, and active smoking	Atrial myxoma	Memory loss, headache, weakness	Middle cerebral artery	Myxoma resection surgery	Thrombectomy	2	2
6	16/M	Migraine and ischemic heart disease	Atrial myxoma	Right hemiparesis, headache, campimetry deficit, initial NIHSS of 16	Internal carotid	Myxoma resection surgery	Thrombolysis	3	3
7	28/F	Unknown	Atrial myxoma	Left hemiparesis, initial N IHSS of 12	Right middle cerebral artery	Myxoma resection surgery	Thrombolysis	3	1
8	40/F	Unknown	Left atrial myxoma	Right hemiparesis and headache	Multiple territories	Myxoma resection surgery	Thrombolysis	0	0
9	36/M	Family history of stroke and ischemic heart disease	Atrial myxoma	Seizures, headache, dizziness, hemiparesis	Middle cerebral artery and lenticulostriate arteries	Myxoma resection surgery	ASA, statins	4	4
10	18/F	Dyslipidemia	Atrial myxoma	Hemiparesis, headache	Left middle cerebral artery	Myxoma resection surgery	Thrombolysis	1	1
11	53/M	Type 2 diabetes, verte brobasilar stroke	Left atrial myxoma	Loss of awake state, deviation of the lip corner to the left, right central facial paralysis, dysarthria, right hemiparesis, motor aphasia,	Multiple territories Posterior communicating artery inferior posterior cerebellar artery	Myxoma resection surgery	Thrombectomy	2	2

M: male; F: female; ASA: acetylsalicylic acid; mRS: modified Rankin Scale.

cases[7]. Therefore, some authors recommend performing annual echocardiographic follow-up after surgery for 4 years[38] to detect recurrence of the disease or new neurological complications. However, since there are reports of recurrence occurring up to 3, 7, or more years later[24,25], and of cerebral aneurysms appearing up to 7 and 25 years after surgery for myxoma[31,39], it is important to actively monitor the patient for a longer period of time.

Case series presentation

A series of cases is presented with the presentation of cerebrovascular disease and cardiac myxoma diagnosed incidentally during the stroke study protocol and treated at a third-level center in Mexico City (Table 1). Eleven patients with a mean age of 37.5 years ± 13.1 at the time of cerebrovascular disease symptoms were included, with a range of 16-54 years. Fifty-five percent (n = 6) were women and 45% (n = 5) were men. All patients presented symptoms consistent with stroke, and up to 18% had a history of transient ischemic attacks before the first ischemic event.

The studies carried out were part of the medical procedures. All patients underwent a brain tomography as part of the initial study protocol for stroke, and an echocardiogram in the early days of hospitalization was performed and interpreted by an echocardiologist. None of the patients were aware of their myxoma diagnosis before the first stroke. In some cases, cerebral MRI and angiography were performed for diagnostic and therapeutic purposes of the stroke. In some patients, CT or CMR was performed as part of the pre-surgical protocol for myxoma resection.

All patients presented with cardioembolic stroke (100%, n = 11), and all were incidentally diagnosed with myxoma during the search for the etiology of the stroke. Initially, thrombolysis was used (54%, n = 6) and mechanical thrombectomy was performed (27%, n = 3) without complications, adjusting the pharmacological treatment with antiplatelet and anticoagulant medications, and subsequently, the myxoma was resected.

The average length of hospital stay during the first stroke event was 10.67 ± 11.8. Up to 64% (n = 7) remained without cardiac symptoms after the resection and during follow-up. Patients were assessed for functional capacity using the modified Rankin Scale (mRS) at discharge and during follow-up at 3, 6, and 18 months. At discharge, 54% (n = 6) had a good functional outcome (mRS < 2 points) and 45% (n = 5) had a poor functional outcome (mRS > 3 points). At 18 months, 64% (n = 7) had a good functional outcome and 36% (n = 4) had a poor functional outcome.

The average follow-up period was 21.5 ± 17.2 months. Among the patients, 18% (n = 2) experienced recurrent strokes, and brain metastasis was found in one of these patients.

Discussion

Although cardiac myxomas have a low prevalence, several case series have been documented in Mexico. The Cardiology Hospital of Centro Médico Nacional Siglo XXI reported 51 primary cardiac tumor cases over 16 years, with 74% being myxomas[40]. The Centro Médico Nacional 20 de Noviembre reported 34 myxoma cases over 11 years[41]. In addition, the Centro Médico ABC also reported 12 cardiac tumor cases over 12 years, where 75.1% were myxomas, occurring more frequently in women at a ratio of 5:1[42]. Our report includes 11 cases recorded over a 25-year period.

Diagnosis and treatment present significant challenges within our country's health systems. Regular long-term follow-up using imaging studies such as echocardiography and MRI is required to detect new tumors or brain lesions. While guidelines recommend a 4-year follow-up[38], numerous cases have been reported beyond this timeframe[39,43].

In our case series, two patients experienced recurrent stroke after myxoma resection. The first patient had three strokes at 3-, 8-, and 24-month post-surgery and the second had two at 5- and 51 months after the myxoma resection. In both cases, follow-up was lost multiple times, which prevented imaging studies from being performed to assess any tumor growth. As a result, we associate tumor growth with the recurrence of stroke.

The risk of recurrent stroke grows with increasing time intervals between the initial cerebral infarction and the surgical resection of the myxoma[44]. In our series, patients with recurrence had a time interval of 2-3 weeks between the first stroke and myxoma resection, and this may have increased the risk of recurrent strokes.

Myxoma resection is the only treatment that can prevent neurological complications[24] since up to 46% of patients with recurrence of cerebral infarction were on antiplatelet or antiplatelet treatment[45]. In our case series, patients were given platelet and anticoagulant treatment in the acute stroke and long-term antiplatelet treatment was implemented.

Treatment of stroke with thrombolysis and thrombectomy seems to be effective treatment with a good

prognosis, especially in the case of thrombolysis. Rao et al. (2022) found in a study involving patients with cerebral infarction and myxoma that the average mRS was 2 for patients treated with thrombolysis and 3 for those treated with mechanical thrombectomy at discharge and at the 3-month follow-up[29,30].

In this case series, six patients underwent thrombolysis treatment. The average mRS at discharge was 2, dropping to 1.6 at the 6-month follow-up. On the other hand, three patients were treated with thrombectomy. The average mRS for these patients was 2.3 at both discharge and the 6-month follow-up. All patients remained free from complications.

Conclusion

Myxomas are a rare cause of cerebrovascular disease. Therefore, it is crucial to identify the cardiac tumor early on to allow for prompt resection as the initial treatment, to prevent neurological complications. Patients who experience a cardioembolic event should undergo a comprehensive diagnostic protocol to determine the cause, such as the presence of a blood clot or embolization due to an intracardiac tumor. Once the diagnosis is confirmed, the stroke is treated, and the myxoma is removed and patients should be closely monitored for any recurrence of the primary tumor and potential subsequent neurological complications.

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REVIEW ARTICLE

Dazed and confused: the neurological examination of the unconscious patient

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Abstract

The neurological examination of unconscious patients is critical in emergency settings, where up to 5% of consultations are due to impaired consciousness. Despite the challenges posed by the lack of patient cooperation, various maneuvers can help establish the cause and localization of neurological issues. This paper presents an approach to the neurological examination in unconscious patients, emphasizing its importance in differential diagnosis and treatment planning.

Keywords: *Clinical exam. Emergencies. Unconsciousness.*

Aturdido y confundido: el examen neurológico en el paciente inconsciente

Resumen

La exploración neurológica de pacientes inconscientes es crítica en entornos de emergencia, donde hasta el 5% de las consultas se deben a alteraciones de la conciencia. A pesar de los desafíos que plantea la falta de cooperación del paciente, varias maniobras pueden ayudar a establecer la causa y localización de los problemas neurológicos. Este artículo presenta un enfoque para la exploración neurológica en pacientes inconscientes, destacando su importancia en el diagnóstico diferencial y la planificación del tratamiento.

Palabras clave: *Examen clínico. Urgencias. Inconsciencia.*

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Introduction

The neurological examination, like any physical examination, aims to prove or disprove the differential diagnosis derived from the patient's history[1]. As a versatile tool, it can be adapted to various scenarios and needs, including the assessment of an unconscious patient.

The classic structured neurological examination largely depends on the patient's cooperation and interaction. While some components (e.g., gait assessment) cannot be performed on an unresponsive or non-cooperative patient, there are still numerous maneuvers that can be conducted to establish the cause and localization of the patient's problem. This is crucial, as up to 5% of all emergency department consultations are due to impaired consciousness. The differential diagnosis in such cases is broad, including seizures, cerebrovascular disease, infections, and intoxications, among others. This underscores the importance of performing an accurate and methodical neurological examination[2,3].

Here, we present our approach to the neurological examination of the unconscious patient focused on adult population. Pediatric examination will not be discussed here (Fig. 1).

History and general physical examination

Several neurological textbooks highlight the importance of history taking and the general physical examination in the inpatient neurological setting[4,5].

For the acute coma scenario, the most important aspects of the history to consider are the onset, past medical history, current list of medications, and context (what was the patient doing?). With these four questions, a clever physician can start formulating their working hypothesis.

The minimum general physical examination involves inspection and vital signs. Since in most hospitals, the first physician to evaluate patients is rarely a neurologist, most patients will be stable, monitored, and will have basic bloodwork by the time a neurological evaluation is required. Abnormalities in respiration are important and can help localize lesions (Fig. 2). The inspection often reveals clues about comorbidities that patients may have, and signs suggesting skull fractures (Battle's sign or raccoon's eyes sign)[4].

Level of consciousness

Consciousness, simply put, involves three main axes: wakefulness, awareness (the ability to interact with the environment), and the ability to produce movement[6]. Impairment in any of these can cause acute or chronic impairment of consciousness, as described in tables 1 and 2[5,7,8].

In chronic cases, it may be difficult to differentiate between a minimally conscious state and a vegetative state (now often referred to as unresponsive wakefulness syndrome). In such cases, the Coma Recovery Scale-Revised is one of the most sensitive tools used to detect disorders of consciousness[9,10].

Cranial nerves

The full cranial nerves examination requires the patient's cooperation, which could lead to the assumption that in unconscious patients, this assessment cannot be done. However, there are useful maneuvers that are even included in brain death criteria and aid prognosis in post-cardiac arrest patients[11,12].

As with the cooperative patient, a systematic approach is often helpful and prevents overlooking important steps.

For the II cranial nerve, fundoscopy can be performed, some authors emphasize that technical difficulties, the time-consuming nature of the examination, and an overall low sensitivity for detecting papilledema in undilated pupils by non-ophthalmologists may render this test less useful in the acute coma setting; nevertheless, it should always be checked[13]. The pupillary light reflex involves the II and III cranial nerves, and its absence can be considered a reliable predictor of poor functional outcome in post-cardiac arrest patients[12].

The blink to threat (also known as the menace reflex) is frequently used in clinical practice. In response to a sudden lateral movement directed toward the eyes, a person momentarily closes their eyelids. There is little information about the sensitivity and specificity of this maneuver. Some authors propose the following rule of thumb: in daily clinical practice, the presence of the menace reflex excludes hemianopia, but its absence is of little localizing value and does not necessarily imply a visual field deficit[14].

The examination of eye movements is one of the most valuable tools for diagnosing neurological disease. Detailed evaluation can help physicians localize lesions and assist in establishing the prognosis for unresponsive patients (Tables 3 and 4).

The rest of the cranial nerves' examination involves evaluating brainstem reflexes (e.g., corneal reflex,

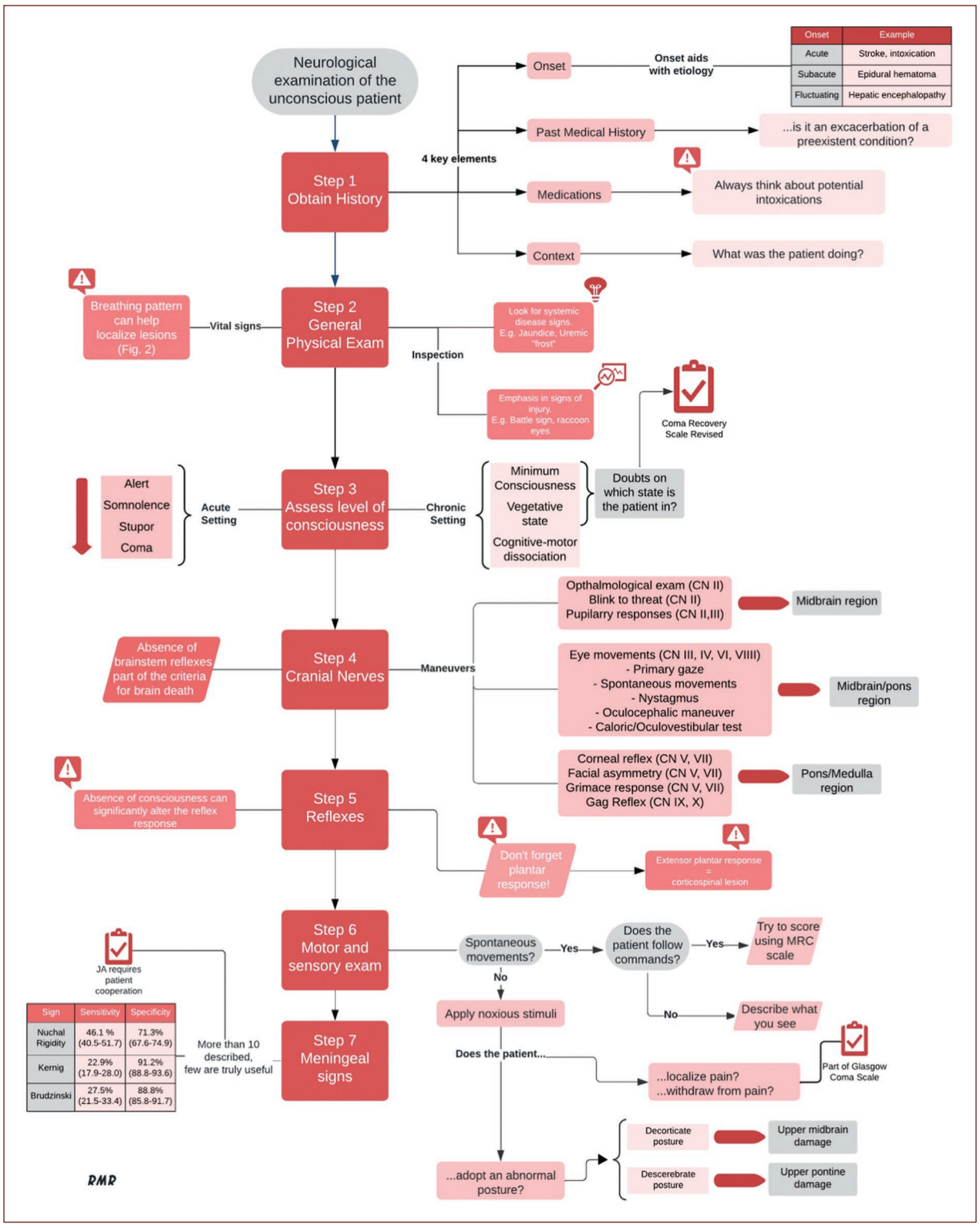

Figure 1. The neurological examination of the unconscious patient.

facial symmetry at rest, grimace response, and gag reflex), which are essential. Their lack of response can also aid in localizing lesions[11,13]. Dude to the need for patient's cooperation, the lower cranial nerve's examination is usually limited to the gag reflex.

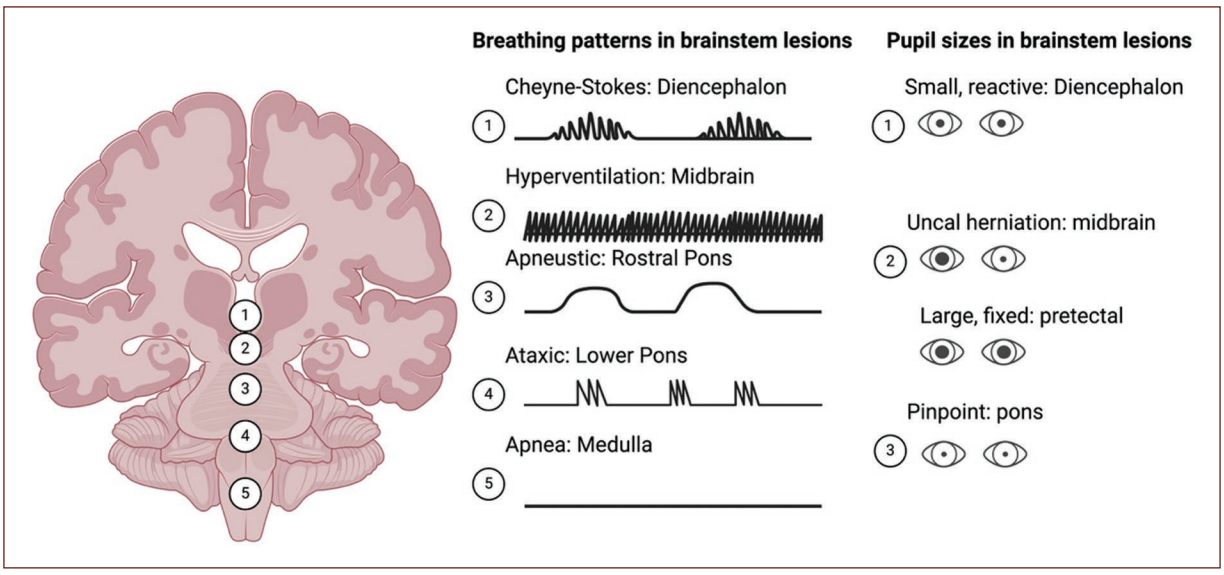

Figure 2. Breathing patterns in brainstem lesions *(adapted from Posner et al., 2019)*[5].

Table 1. Acute unconscious states definitions

Conscious state	Definition
Alert	The subject is awake. Full awareness of self and one's relationship with the environment is required
Somnolence	A condition characterized by diminished alertness where the individual tends to nod off when not actively engaged
Stupor	A *deep-sleep* like state wherein the person can only be aroused with intense and sustained stimulation
Coma	The individual lies with eyes shut and despite of the vigorous stimulation (*e.g., painful stimuli*), the individual cannot be aroused

Adapted from Posner et al., 2019[5]

Table 2. Chronic unconscious states definitions

Conscious state	Definition
Minimum consciousness	The subject shows sporadic or minimal but clear evidence of self or environmental awareness which is consistently demonstrated (e.g., purposeful behavior)
Vegetative state	There is absence of behavioral evidence of awareness of the self and the relationship with the environment. There remains the stimulus-induced arousal and normal sleep-wake cycles
Cognitive-motor dissociation	Also known as covert consciousness. Detection of intentional brain activity through MRI or EEG, but no response to the examiner and no detectable command following behaviors

Adapted from Posner et al., 2019[5]

Reflexes

Reflexes in unconscious patients may not be as critical as in cooperative patients, but their absence in acute settings (< 24 h) may indicate a spinal cord injury. Over time, the natural course is for these reflexes to become exaggerated (hyperreflexia), which is commonly seen in the progression of spinal cord injuries[15].

Monosynaptic reflexes, also known as stretch reflexes, involve a single synapse between the afferent (sensory) and efferent (motor) neurons. The most recognized one is the patellar or knee-jerk reflex. This reflex examination involves striking the patellar tendon with a reflex hammer. A typical response is the contraction of the quadriceps muscle, causing extension of the leg. Absence or reduction of this reflex may suggest a lesion at the L2-L4 level of the spinal cord. Other important localizing reflexes include the bicipital (C5-C6), brachioradialis (C6), tricipital (C7), and ankle-jerk (S1) reflexes[16]. Cranial to caudal inspection order is always recommended.

Polysynaptic reflexes, on the other hand, involve multiple synapses and interneurons, providing a more complex response. The nociceptive flexion reflex, commonly examined in unconscious patients, is believed to be a polysynaptic reflex aimed at facilitating the withdrawal of

Table 3. Eye movement maneuvers in non-responsive patients

Eye movement	Description
Primary gaze	Primary gaze refers to the resting position of the eyes, looking forward without specific eye movements. Dysconjugate eyes indicate lesions affecting individual nuclei located in the brainstem
Spontaneous eye movements	Spontaneous eye movements are the natural, effortless eye movements that occur without conscious effort
Nystagmus	Nystagmus is an involuntary, rhythmic eye movement that can be horizontal, vertical, or rotatory. It can be a sign of neurological or vestibular conditions
Oculocephalic maneuver	The oculocephalic maneuver, also known as the doll's head test, is used to assess vestibular function. It involves turning the patient's head while observing eye movements. Abnormal horizontal doll's head eye movements are indicative of lesions affecting oculomotor nerves (III), abducens nerves (VI), and pons. Abnormal vertical doll's head movements are indicative of lesions affecting oculomotor nerves (III), trochlear nerves (IV), and midbrain
Caloric tests	Caloric tests are used to assess vestibular function by stimulating the inner ear with cold or warm water. The patient's eye movements are observed in response to temperature changes in the inner ear

the biceps femoris muscle in response to noxious stimulation[17]. This reflex involves a multilevel area of the spinal cord and the integrity of multiple sensory and motor pathways[18]. Other helpful localizing polysynaptic reflexes include the abdominal cutaneous (T9-T11), cremasteric (L1-L2), bulbocavernosus (S2-S4), and anal wink (S2-S4) reflexes[19-21].

The Babinski sign, another crucial examination, is assessed by stimulating the sole of the foot and observing toe movements. An extensor response is considered abnormal and indicates a corticospinal lesion[22]. Several alternate methods for eliciting an extensor response exist, with the Chaddock and Oppenheimer signs being the most useful variations of the Babinski sign with a sensitivity of 50% but with a specificity of 99%[4,23].

An exaggeration of reflex responses, including abnormal posturing (decerebrate or decorticate), can indicate severe brainstem dysfunction, as will be discussed in the motor examination[5].

Motor and sensory examination

Examining unconscious patients poses unique challenges, as these patients are unable to provide feedback or follow commands. Therefore, the sensory and motor examination techniques employed must be tailored to these circumstances. Motor examination starts with inspection to determine spontaneous or reflex movements[5]. If a patient follows verbal commands, the Medical Research Council score is recommended for motor evaluation. If the patient has spontaneous movements but does not respond to verbal commands, only a description of abnormal movements is recommended.

Tone examination can be done, but we should always remember that in a physiologic state, the tone is diminished during sleep states; however, passive movement can reveal chronic tone changes such as spasticity[24].

In unconscious patients or those without spontaneous movements, motor response to vigorous stimuli should be elicited. These stimuli include pressing the orbital roof, performing a sternal rub, or stimulating the periungual region. Decerebrate or decorticate posturing helps infer the level of brainstem or cerebral dysfunction[5]. Decorticate posturing is characterized by flexion of the elbows and wrists with extension of the legs and feet, while decerebrate posturing is characterized by rigidity and sustained contraction of the extensor muscles of all four extremities. Decorticate posturing is produced by extensive lesions from the forebrain to the rostral midbrain. In contrast, decerebrate posturing is associated with upper pontine lesions, indicating the release of vestibulospinal reflexes. Decerebrate posturing is usually more severe than decorticate posturing, as patients are less likely to recover. Abnormal posturing is associated with a worse prognosis, with only 37% of decorticate patients surviving following a head injury and only 10% of patients with decerebrate posturing[25].

Some patients can have abnormal postures in response to sensory stimuli such as the "Lazarus sign" where in response to neck flexion the upper limbs move and can adopt a dystonic-like posture[26].

Sensory examination in unconscious patients is more intricate because it heavily relies on patient feedback, which is not feasible in this scenario. The Glasgow coma scale (GCS) is commonly used, focusing on eye-opening, verbal, and motor responses to stimuli, providing indirect inferences about sensory function. Although GCS does not specifically measure sensory input, abnormal responses usually correlate with severe sensory impairment[27]. Since the clinical evaluation

Table 4. Eye movement findings in lesions at specific levels of injury

Eye movement	Midbrain lesion	Pons lesion	Medulla lesion
Primary gaze	Impaired horizontal and vertical gaze control due to disruption of the midbrain's superior colliculus and cranial nerve nuclei. Convergence may also be affected	Impaired horizontal gaze control due to damage to the abducens nucleus. Vertical gaze may remain intact. Convergence may be impaired	Severely impaired horizontal and vertical gaze control due to extensive involvement of cranial nerve nuclei and pathways. Convergence is often lost
Spontaneous eye movements	Generally preserved as the midbrain lesions tend to spare the vestibular and brainstem reticular formation. Spontaneous nystagmus may occur	May exhibit spontaneous nystagmus due to disruption of vestibular pathways, but some preservation of spontaneous eye movements is possible	Often severely impaired due to extensive brainstem involvement. Spontaneous nystagmus is common, and spontaneous eye movements may be limited
Nystagmus	Depending on the location of the lesion within the midbrain, various forms of nystagmus can occur, including vertical, rotatory, or gaze-evoked nystagmus	Horizontal nystagmus, often with a specific pattern based on the affected pontine structures, such as horizontal gaze palsy with pontine lesions (HGPP)	Horizontal nystagmus, typically horizontal gaze palsy with pontine lesions (HGPP), but may also involve other patterns
Oculocephalic maneuver	May show impaired or absent oculocephalic reflex (doll's head maneuver) due to disruption of the superior colliculus and oculomotor pathways	Oculocephalic reflex may still produce some eye movement, but it can be altered or diminished	Oculocephalic reflex is often absent or severely impaired, reflecting extensive brainstem damage
Caloric tests	Cold caloric tests may reveal reduced or absent nystagmus due to impaired vestibulo-ocular reflex (VOR). Warm caloric tests may produce minimal response	Cold caloric tests may yield reduced nystagmus or directional changes due to damage to vestibular nuclei. Warm caloric tests may show diminished response	Both cold and warm caloric tests typically result in minimal to no nystagmus, indicating severe vestibular dysfunction

of the sensory system is limited in this scenario, evoked potential studies are useful in evaluating the functionality of sensory pathways. In this procedure, sensory stimuli are delivered, and the subsequent brain electrical responses are recorded[28].

Meningeal signs

Central nervous system infections are life-threatening conditions that can present as disturbances in consciousness in the emergency department[3]. Clinical diagnosis is one of the most difficult topics in neurology, and due to this, several signs have been described to aid in its diagnosis[29]. Most of these signs lack enough sensitivity and specificity to confidently rule in or out meningitis. Inconsistency between studies, uncertain microbiology (sometimes confounded by pretreatment with antibiotics), and interobserver variability are some reasons why a high suspicion of a central nervous system infection is needed when interpreting these signs[30].

The most useful signs are Jolt Accentuation, nuchal rigidity, and Kernig and Brudzinski's signs. Their sensitivity is low, but they are highly specific, which makes them very practical when present[30,31].

Other reflexes

Primitive reflexes (those that are present in early life, but are suppressed by development), also so-called frontal release reflexes (e.g., palmomental reflex and palmar grasp) are rarely useful since they are found in healthy people and rarely help in determining the localization and etiology of the problem. However, a very exaggerated release reflex does help pointing to a brain disease[32].

Conclusion: order even in chaos

The purpose of our approach is to avoid biases and promote a systematic evaluation of patients in the acute setting at the emergency room. Nowadays, there are clinical scales (e.g., FOUR scale) designed to standardize the evaluation of patients and facilitate communication between specialists. These scales are useful but were designed for particular settings, such as intubated patients, and not as a first evaluation in the emergency department[33].

Since impaired consciousness is a frequent reason for consultation in neurology and has several differential

diagnoses, clinical examination remains crucial in the diagnostic and therapeutic process.

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Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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REVIEW ARTICLE

A review on the spectrum of atrial fibrillation detected after a stroke

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Abstract

This article reviews the concept of atrial fibrillation (AF) detected after a stroke (AFDAS) as a potentially different entity than known AF (KAF). For this, we describe the pathogenesis of neurogenic AF, the relevance of stroke induced heart injury, and other mechanisms in the development of AFDAS as opposed to a cardiogenic mechanism in KAF. Later, we will highlight the differences in characteristics and prognosis of KAF and AFDAS and provide existing evidence that supports the importance of this differentiation for clinical practice and future research.

Keywords: *Atrial fibrillation. Stroke. AFDAS. Pathophysiology.*

Una revisión del espectro de fibrilación auricular detectada después de un ataque cerebrovascular

Resumen

Este artículo revisa el concepto de Fibrilación auricular (FA) detectada después de un ACV (AFDPA) como una entidad potencialmente diferente a la AF conocida (AFC). Para esto describimos la fisiopatología de la AF neurogénica, la relevancia de la lesión cardiaca inducida por ACV (LCIA), y otros mecanismos del desarrollo de AFDPA en oposición al mecanismo cardiogénico de la AFC. Posteriormente, resaltamos las diferencias en características y pronóstico de la AFC y AFDPA y proveemos la evidencia existente que soporta la importancia de esta diferenciación en la práctica clínica y para la investigación a futuro.

Palabras clave: *Fibrilación auricular. Ictus. AFDPA. Fisiopatologia.*

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Introduction

Atrial fibrillation (AF) affects 2-4% of global population[1]. It is characterized by poor contractility, increased automaticity, decreased refractoriness, and re-entry activity[2]. The strong association between AF and ischemic stroke was stablished decades ago, with studies showing an increased risk of stroke in patients with AF (≅ 5 times higher), and a high prevalence of AF in patients with ischemic stroke (≅ 20 to 30%)[3]. Recent studies on sequential heart rhythm evaluation in post-stroke patients have shown that AF can be diagnosed *de novo* in up to 20% of post-stroke patients, half of the diagnosis are made during the hospitalization period, and an additional 11% is diagnosed in the early post-hospitalization months[4]. Previously, the association between AF and stroke was considered to be unidirectional (e.g., AF as the cause of cardioembolic stroke). More recently, the relationship between these two entities has been shown to be more complex than that, as AF and stroke can possibly coexist as bystander and can even be the consequence of a recent stroke through a pathophysiological pathway involving inflammation, autonomic dysfunction and the so-called stroke-Induced Heart Injury (SIHI), as one of the clinical expressions of the stroke-heart-syndrome (SHS)[5].

AF pathophysiology

Most AF cases occur in the context of abnormal atrial substrate (also called atrial cardiopathy) that encompasses chronic structural, electrical, and hemodynamical derangements of the left atrium. This type of AF has been called cardiogenic AF because it entirely depends on cardiac disease[6]. Age is the strongest risk factor for cardiogenic AF, with a yearly increase in prevalence of approximately 5% after the age of 65[7]. AF is more frequent in Caucasians compared with non-Caucasians[8]. Mutations and certain gene polymorphisms for ion channels, transporters, and structural components of myocytes, have been associated with the disease[9,10]. Other conditions associated with AF are cardiovascular risk factors such as hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, and sleep disordered breathing; acute illnesses such as surgery or sepsis; and cardiovascular comorbidities, including coronary artery disease, heart failure, valvular heart disease, and left ventricular systolic disfunction[11-13]. Finally behavioral or social factors such as smoking, alcohol use, obesity, unhealthy dietary habits, sedentary lifestyle, and intense physical activity, are also associated with increased AF risk[11,14]. The multiple atrial abnormalities established in this setting include structural remodeling, abnormalities in calcium handling, fibrosis and conduction slowing and blockade pathophysiological routes which all account for the development and maintenance of arrhythmogenesis[15].

AF can also be secondary to a stroke, as it is one of the manifestations of the SHS, in which case it is called neurogenic AF. Other manifestations of SHS include electrocardiography (ECG) changes (e.g., QT prolongation), heart failure, acute coronary syndrome, Takotsubo syndrome, and sudden death[6,16]. Mainly based on research in animals, three main mediators to SIHI has been described: the first one is an immunological cascade including systemic inflammatory response, pro-inflammatory cytokines, and macrophage infiltration[17]. The second is humoral changes, mainly on norepinephrine levels and catecholamine production systemically and in cardiac tissue respectively[18]. The third mediator is neuronal, where direct damage to the central autonomic network including the insular cortex, amygdala, anterior cingulate cortex, ventromedial prefrontal cortex, etc., is associated with autonomic dysfunction and altered cardiac autonomic control through Vagus nerve and paravertebral ganglia with subsequent arrhythmogenic effects on cardiomyocytes[19]. Stablished risk factors for SHS are stroke severity, stroke involvement of the central autonomic network (especially the insular cortex), age, and previous history of coronary or structural heart disease[16].

Atrial fibrillation detected after stroke (AFDAS)

Rhythm evaluation is a vital step in the study for stroke etiology. ECG, telemetry, Holter, and long-term monitoring are often used to detect AF in patients without a previous diagnosis of it; finding AF in a patient with a history of a stroke usually is considered an indication for oral anticoagulation (OAC)[1]. If AF is newly detected after a stroke, at least two possibilities must be considered: the patient had a previously undetected AF probably secondary to cardiac abnormalities and atrial cardiopathy, or the patient had never had AF before and developed AF as a consequence at least partially of the stroke[20].

Studies comparing AFDAS versus known AF (KAF) in stroke patients have shown that these populations have different baseline characteristics. Patients with AFDAS are healthier than KAF patients: a meta-analysis showed that they have fewer cardiovascular risk factors (hypertension, dyslipidemia, coronary artery disease, prior myocardial infarction, congestive heart failure, peripheral

artery disease and previous stroke or TIA), and fewer cardiac functional or structural abnormalities (left atrial (LA) diameter, left ventricular ejection fraction)[21].

On the other hand, there is evidence supporting that AFDAS patients have larger strokes, higher NIHSS, and higher proportion of insular involvement than both patients with KAF and patients in sinus rhythm[22,23]. AFDAS also seems to occur more frequently among ischemic stroke than in transient ischemic attack patients[24], which aligns with the concept that more severe strokes, which more extensive and definite involvement of the central autonomic network (CAN) would be more likely to be associated with more SIHI. Interestingly, AFDAS status compared to KAF and no-AF has been shown to be associated with additional ECG and echocardiographic markers of SIHI, such as troponin I levels, heart failure (acute or exacerbated), acute coronary syndrome and clinically relevant arrhythmias in post-stroke patients, even after the adjustment for confounders[25]. In the latter study, LA volume index was also associated with AFDAS.

Several markers have been described in association with atrial cardiopathy. These include LA strain, LA size, p-wave terminal force in V1, natriuretic peptides levels, and cardiac troponin levels among many others[6,26,27]. Atrial cardiopathy seems to play a role as facilitator of arrhythmogenesis in AFDAS, just as it does for AF development in patients without a stroke[28]. A "rise and fall" pattern of cardiac troponin typical of acute myocardial injury instead of chronically increased troponin more characteristic of chronic myocardial injury is a biomarker that may be used to differentiate patients with SIHI and probable neurogenic AFDAS from patients with chronic cardiac abnormalities with probable cardiogenic AFDAS[29]. This concept remains to be proven. It seems plausible that KAF and AFDAS patients with a more abnormal atrial substrate share a predominantly cardiogenic physiopathology, and AFDAS patients with a previously normal or close to normal atrial substrate and markers associated to SIHI have a predominant neurogenic physiopathology (neurogenic AFDAS). Atrial cardiopathy may be a facilitator for AF development after a stroke in patients without previous AF.

A recent meta-analysis found that increasing age, female sex, hypertension, NIHSS score, previous stroke, intravenous thrombolysis, brain natriuretic peptide, and high-density lipoprotein levels are associated with AF detection after stroke; and smoking, low-density lipoprotein, and triglyceride levels are associated with no AF detection after stroke[30]. Other studies have also considered ischemic heart disease, LA enlargement, heart failure, and troponin levels as risk factors for AFDAS. A summary of the different markers and predictors of AFDAS, SIHI, and atrial cardiopathy is shown in figure 1.

It must be noted that patients with AF detected on admission ECG do not behave the same as the rest of AFDAS patients[31]. Studies have shown that baseline characteristics and the risk of recurrent stroke are similar to that of patients with permanent AF, so the current recommendation is to consider these patients as not having AFDAS, but a higher burden AF, as they probably have a previously unrecognized AF[32].

AFDAS as an incidental finding

Prolonged cardiac monitoring in patients with subclinical AF and incident ischemic stroke during monitoring have shown that up to 70% of strokes do not have temporal relationship with arrhythmic episodes. In addition, long-term continuous cardiac monitoring in patients with ischemic stroke secondary to large- or small-vessel disease have an AF detection rate of up to 12% in a year[33,34], similar to that found in patients with cryptogenic stroke[35]. This highlights the fact that the detection of AFDAS does not necessarily mean that AF was the etiological determinant for the stroke, and it can be either a bystander or a consequence of the stroke.

Implications of differentiating AFDAS from KAF

There are differences in prognosis between KAF and AFDAS. AFDAS patients have lower AF burden, concept supported by the high proportion of AFDAS episodes lasting < 30 s, having lower rates of sustained AF, and higher rates of spontaneous conversion to sinus rhythm[23,36]. These findings are probably associated to the lower burden of atrial cardiopathy, which is known to have a role in maintaining and perpetuating AF[37]. Additionally, a more benign risk profile of AFDAS has been demonstrated with a lower risk of recurrent stroke than in KAF by around 26%, but with a risk of death not clearly lower. Conversely, the risk of recurrent stroke in AFDAS is twice as high as the risk of patients with no-AF and the risk of death in AFDAS is around 60% higher than that of patients with no-AF[21,29,38,39]. As a consequence, the risk profile of AFDAS as a whole seems to be located somewhere in the middle between KAF and no-AF. The relatively lower embolic risk of AFDAS is explained by the interplay between AF burden, but a lower severity of underlying atrial cardiopathy (e.g., lower prevalence of LA enlargement), and a lower prevalence of other cardiovascular risk factors[29].

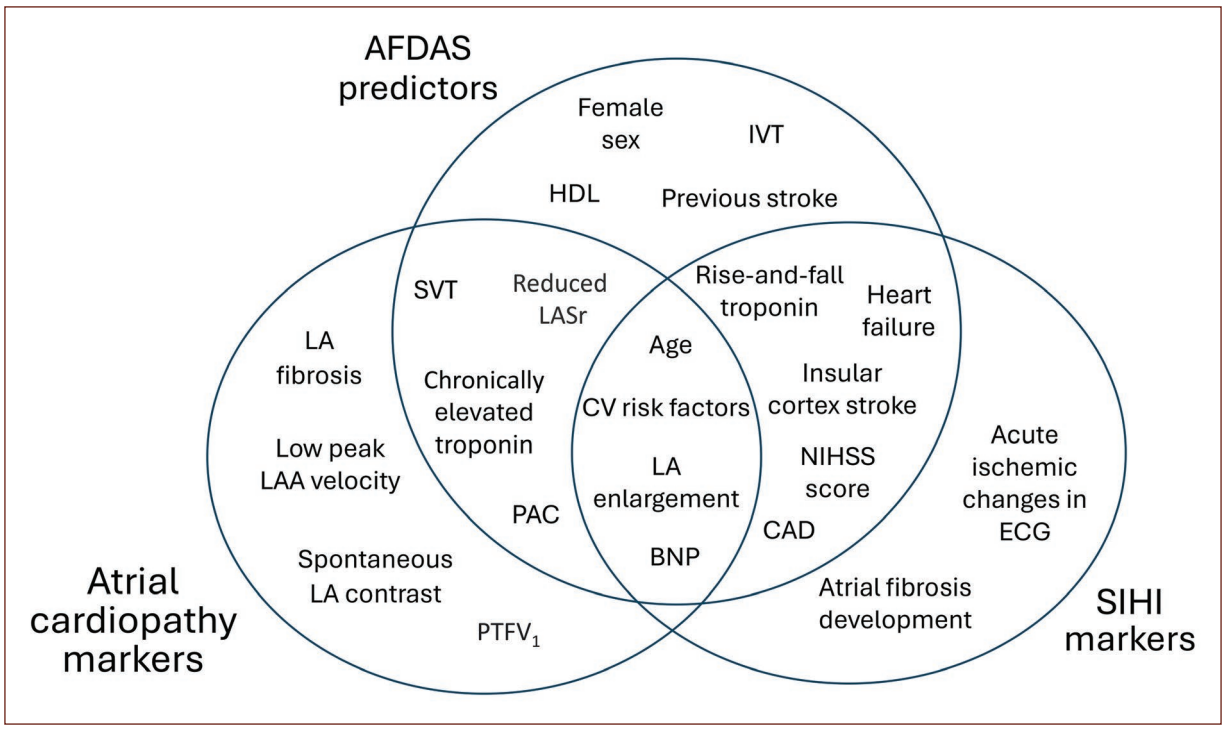

Figure 1. Atrial cardiopathy, stroke-induced heart injury, and atrial fibrillation detected after a stroke proposed markers and predictors. Many of these markers are shared between the three entities. BNP: brain natriuretic peptide; CAD: coronary artery disease; HDL: high density lipoprotein; IVT: intravenous thrombolysis; LASr: left atrial reservoir strain; PAC: premature atrial complexes; PTFV1: P-wave terminal force in lead V1; SVT: supraventricular tachycardia.

AF secondary to thyrotoxicosis has a similar behavior than AFDAS. Studies have shown lower risks of all-cause mortality and ischemic stroke (HR: 0.66, and 0.73 respectively, both with $p < 0.0001$) in patients with thyrotoxic AF compared with non-thyrotoxic AF patients[40]. This supports the idea of non-cardiogenic AF to have a lower thromboembolic risk than cardiogenic AF again probably because of a more normal atrial substrate and lower frequency of cardiovascular risk factors.

A retrospective study showed that OAC is effective in preventing recurrence of stroke in AFDAS patients compared to no-OAC without a significant increase in hemorrhage, but this study was likely based on patients with high burden AF based on a short duration of monitoring for its detection[41]. A recent meta-analysis on prolonged cardiac monitoring-detected AFDAS failed to demonstrate efficacy of this strategy for prevention of ischemic stroke recurrence[29]. To date non-differentiated AFDAS is treated the same way as KAF, and OAC is usually initiated. This approach is further supported by the recent results of the ARTESIA clinical trial, which showed that apixaban reduced the risk of stroke and systemic embolism in patients with device-detected subclinical AF compared to Aspirin[42].

In figure 2, there a schematic representation of the continuum of neurogenic AFDAS, cardiogenic AFDAS and KAF, its baseline characteristics, risk of stroke, and potential benefit from OAC.

Gaps in knowledge

It is challenging to differentiate whether AFDAS is more likely to have neurogenic origin rather than a cardiogenic origin. A *black-or-white* approach to this matter is also probably wrong, as true AFDAS most likely depends on the interplay of both neurogenic and cardiogenic factors[22]. A better understanding on atrial cardiopathy and SIHI markers is needed, as the accurate detection of these entities is a promising strategy to help us determine the pathophysiology underlying an individual's AFDAS and probably improve prognostic and therapeutic approaches.

Possibly, neurogenic AFDAS would require different therapeutic approaches from KAF. Indeed, patients with AFDAS may benefit from early rhythm control[43]. Steroids, statins, β-blockers, renal sympathetic innervation, aldosterone antagonist and renin inhibitors, has been proposed to potentially interfere with AF development in other scenarios and may be used in post stroke patients[20,44-46].

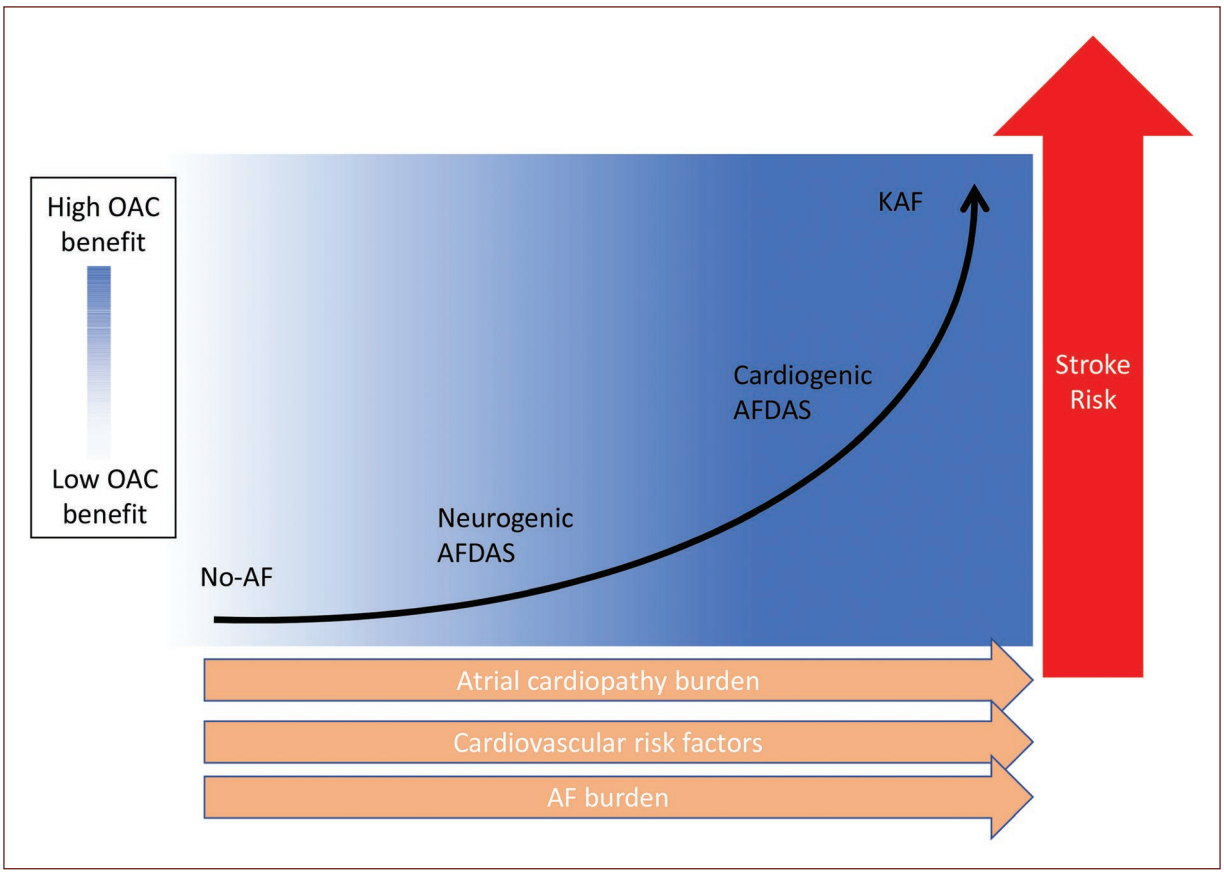

Figure 2. Representation of the spectrum of the disease in AFDAS, where cardiogenic AFDAS is most closely related to KAF in terms of baseline characteristics, burden of the arrhythmia and risk of stroke and neurogenic AFDAS represents a milder entity than both cardiogenic AFDAS and KAF. AF: atrial fibrillation; AFDAS: atrial fibrillation detected after stroke; KAF: known atrial fibrillation; OAC: oral anticoagulation.

Current practice is to use anticoagulation in most AFDAS patients, but data is lacking to determine if selected patients with AFDAS of low embolic risk (low AF burden, few cardiovascular risk factors) may not surpass the currently established threshold for the use direct oral anticoagulants of a ischemic stroke rate > 0.9%/year[47]. Furthermore, current American Heart Association AF management guidelines strongly recommend using anticoagulants in patients with AF and an estimated annual risk of stroke ≥ 2%. It is likely that the majority of cardiogenic AFDAS will benefit from OAC as it is more closely related to KAF, but it is not clear if the subgroup of neurogenic AFDAS has a low enough risk of stroke recurrence where OAC may not be needed. A "pill in the pocket" anticoagulation regime using continuous cardiac monitoring and intermittent periods of anticoagulation when AF is detected may be an alternative approach[48]. Another option would be to use stricter criteria for starting anticoagulation based on higher CHA_2DS_2-VASc score or higher burden of the arrhythmia.

Finally, if AFDAS is detected shortly after the stroke, does it mean that it represents a high-burden AF? or is it because the first few days after a stroke is the period where the manifestations of the SHS are on its peak? Close follow-up to better measure the burden of AF in probably neurogenic AFDAS patients is a possible option to determine if its burden is significant enough to require OAC.

Conclusions

AFDAS constitutes a spectrum of a frequently progressive disease. At the one end, there are patients with lower burden of cardiac abnormalities and cardiovascular risk factors at baseline, where stroke-mediated neurogenic mechanisms could have had more impact on AFDAS development. Some of these patients may

be incidentally diagnosed with AF by applying post-stroke prolonged cardiac monitoring at a very early stage of disease[49]. Others may experience short bursts of neurogenic AFDAS as a transient and self-limited phenomenon. At the other end, there are patients with higher burden of cardiac abnormalities and cardiovascular risk factors before the stroke, in whom cardiogenic mechanisms were probably the cause of asymptomatic AF some time before the stroke, but only recognized after the cerebrovascular event. Recognizing this disease spectrum opens the possibility of offering different therapeutic approaches for neurogenic AFDAS, using maybe more rigorous burden measurement strategies, or a higher threshold for OAC initiation than for cardiogenic AFDAS and KAF. Most importantly, the future research exploring the AFDAS concept may help understand the pathophysiology of AF, both in patients with and without stroke.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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