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FACULTÉ DE MÉDECINE ET DE PHARMACIE

SILENT ISCHEMIC STROKE IN PATIENTS WITH RHEUMATIC VALVULAR HEART DISEASE

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A great emotion and a deep respect for you. Today, we have the honor to write this modest word in order to return homage to our teachers who guided us and always made efforts to our learning and training in both practice and theory formation. These few lines are not enough to express, dear teachers, my great recognition and my deep gratitude for your human and professional qualities which will certainly serve as an example in my career. We remain forever grateful and sincerely respectful to you

SUMMARY

ABSTRACT

Background:

Cardioembolism is responsible for around 20% of ischemic stroke. Cardioembolic infarcts are generally more serious and tend to recur earlier and more frequently than ischemic stroke from other causes. Valvular heart disease is the second cause of cardioembolic stroke after non valvular atrial fibrillation. Ischemic brain lesions can go unnoticed clinically. It is all the more important to recognize them in order to prevent recurrences which can be fatal.

Objective:

The aim of this study is to determine the prevalence of silent ischaemic stroke associated with valvular heart disease, to determine the impact of the existence of an intercurrent atrial fibrillation on valvulopathy and to specify the echographic abnormalities observed in valvular patients who developed silent ischaemic stroke and the impact of anticoagulant therapy and the quality of monitoring of the INR on the occurrence of silent ischemic stroke.

Methods:

It's a prospective study of 31 patients followed for valvular heart disease who have benefit from brain imaging in search of a silent brain infarction. The study is carried out in cooperation with the cardiology department of the El Ghassani provincial hospital, the neurology and radiology departments of the Hassan II university hospital of Fez.

Results:

The mean age of our patients was 46 years. 61% of the patients were female. 23% of the patients were in sinus rhythm. The other patients (77%) had atrial fibrillation. 74.19% of the patients had moderate to severe mitral

stenosis. 64.51% of the patients had an enlarged left atrium with more than one valvulopathy. The mean ejection fraction was 56%. 84% of the patients were under anticoagulation therapy. 45.16% of our patients had a labile INR. All patients underwent brain MRI (DWI, FLAIR and T2 * weighted sequences) showing cortical- subcortical infarct in 45.20% of cases, Watershed infarct in 3.2% of cases, lacunar infarct in 3.2% of cases and Hemorrhagic lesion in 6.5% of the patients. 38.70% of cases had a normal brain MRI.

Conclusion:

Our study had evaluated the clinical, biological and radiological features of the patients with valvular heart disease who are at the risk of having silent ischemic stroke. That will allow them to be better managed. The study had evaluated the various therapeutic alternatives in order to prevent the occurrence of clinically ischemic stroke and its serious consequences on these patients.

Key words: rheumatic valvular disease- Brain MRI- silent stroke.

INTRODUCTION

Silent ischemic stroke is defined as an asymptomatic infarct detected on cerebral computerized tomography (CT) or magnetic resonance imaging (MRI) in patients with no history of stroke. The silent character of these lesions relates either to their small size and location in truly silent brain areas or to their production of a minor deficit that may have gone unreported and unrecognized as a stroke (1).

Several studies have examined and observed a significant relationship between the frequency of asymptomatic brain lesions and cerebrovascular risk factors including hypertension, carotid artery lesions, atrial fibrillation and diabetes (2). It was also reported that cardiogenic microemboli might also cause similar cerebral lesions (3).

Valvular heart disease is the second cause of cardioembolic ischemic stroke after non-valvular atrial fibrillation.

The aim of this study is to determine the prevalence of silent ischaemic stroke associated with valvular heart disease, to determine the impact of the existence of an intercurrent atrial fibrillation on valvulopathy and to specify the echographic abnormalities observed in valvular patients who developed silent ischaemic stroke.

MATERIALS AND METHODS

1. Framework of the study:

The study is carried out in cooperation with the cardiology department of the El Ghassani provincial hospital, the neurology and radiology departments of the Hassan II university hospital of Fez.

2. Type of the study:

It's a prospective study of 31 patients followed for valvular heart disease who have benefit from brain imaging in search of a silent brain infarction.

3. Study assessment criteria:

The following risk factors were recorded: age, sex, hypertension ((known hypertension treated with anti-hypertensive medication), diabetes mellitus (known diabetes treated with diet and/or medication), hyperlipidemia (known treated hyperlipidemia) and history of smoking.

All patients underwent anamnestic evaluation, general, cardiological and neurological examination at the neurology department.

All patients had at least one electrocardiogram. The diagnosis of atrial fibrillation had been confirmed by an electrocardiogram showing either absent P waves or atrial flutter with an irregular ventricular response.

All patients should have a transthoracic echocardiography showing a rheumatic valvular disease. The following features were recorded: mitral stenosis (defined as rheumatic valvular disease with increased velocities over the valve and a mitral valve area of less than 2.5 cm^2), mitral insufficiency, aortic stenosis (a pressure gradient exceeding 16 mm Hg), mitral, tricuspidal

or aortic valve prosthesis; enlarged left atrium (45 mm or more) and left ventricular ejection fraction. All diameters used were measured according to the recommendations of the American Society of Echocardiography (4-5-6). The embolic risk was defined by cardiologists.

Patients with high risk of embolism were treated with anticoagulants (vitamin K antagonist). Monitoring oral anticoagulation therapy was made by a monthly dosage of the International Normalized Ratio (INR). The target INR is 2 with therapeutic range between 2 and 3 for patients without valve prosthesis. Therapeutic range of INR is between 2.5 and 4 for patients with valve prosthesis depending on patient risk factors and the thrombogenicity of the prosthesis. An INR which is beyond the therapeutic range was considered as labile according to the European Society of Cardiology (7).

A brain MRI with 1.5 Tesla system was performed in all patients. The MR images consisted of DWI, FLAIR and T2* weighted images. All MR images were described by the same radiologist with no knowledge of the patient's clinical data. Low density areas that were sharply demarcated from the surrounding tissue in whole slices were designated as silent infarctions. The size and localization of each lesion were also recorded. We distinguish territorial and lacunar infarcts. Territorial infarcts include lesions affecting a part of cerebral cortex or subcortical lesions. Watershed infarcts were defines as border zone hypo-intensities between arterial territories. Lacunar infarcts were compatible with the occlusion of a single perforating artery (small-deep lesions between 5-15 mm localized at basal ganglions, thalamus, internal and external capsules, and brain stem). Hypointense foci at T2* weighted sequence was defined as hemorrhagic lesions.

All participants provided their written informed consent. The ethical committee of the Hassan II university hospital approved the study (N°: 28/16).

4. Exclusion criteria:

- Patients with history of ischemic stroke or transient ischemic attack.
- Patients with abnormal neurological examination (motor, sensory or verbal dysfunctions).
- Patients carrying a prosthetic valve of which the type of prosthesis contraindicates MRI.
- Patients who refused to participate in the study.

5. Statically Analysis:

Patient's characteristics were expressed as percentages for the qualitative variables and mean for the quantitative variables. Baseline characteristics were compared using Fisher's exact test. P values <0.05 were considered statistically significant. All statistical analyses were performed with SPSS software version 20 (SPSS Inc., Armonk, New York).

RESULTS

1. Age and sex:

The mean age of patients was 45.52 years ± 12.21 with extremes from 24 to 67 years. 24 (77.4%) of patients were under 55 years old.

19 (61.3%) of patients were female and 12 (38.7%) were male with a feminine predominance (61.3%). Sex ratio: 1.58.

Table 1: The age range and sex of patients

Patients		Number	Percentage
Age	≤ 55	24	77.4%
	> 55	7	22.6%
	Total	**31**	**100%**
Sex	Male	12	38.7%
	Female	19	61.3%
	Total	**31**	**100%**

2. Risk factors:

3 patients (9.7%) had hypertension. 2 patients (6.5%) had diabetes mellitus. 8 patients (25.8%) had history of smoking and none of the patients had hyperlipidemia.

Table 2: risk factors of patients

Risk factors	Number	Percentage
Hypertension	3	9.7%
Diabetes mellitus	2	6.5%
Smoking	8	25.8%
Hyperlipidemia	0	0%

3. Cardiac rhythm (electrocardiography):

23 patients (74.2%) were with chronic atrial fibrillation. 8 patients (25.8%) were with sinus rhythm.

Table 3: Cardiac rhythm of patients

Electrocardiography	Number	Percentage
Chronic atrial fibrillation	23	74.2%
Sinus rhythm	8	25.8%
Total	**31**	**100%**

4. Echocardiographic features:

23 patients (74.2%) had a mitral stenosis of which 12 patients (38.7%) had a moderate stenosis and 11 patients (35.5%) had severe stenosis. 5 patients (16.1%) had a mitral regurgitation and 3 patients (9.7%) had an aortic stenosis. 18 patients (58.1%) had more than one valvular disease. 24 patients (77.4%) had an enlarged left atrium. No one had valve prosthesis in our series. The mean left ventricular ejection fraction was 56%.

Table 4: Echocardiography features of patients

Echocardiographic features	Number	Percentage
Valvular disease	**31**	**100%**
Moderate mitral stenosis	12	38.7%
Severe mitral stenosis	11	35.5%
Mitral regurgitation	5	16.1%
Aortic stenosis	3	9.7%
Enlarged left atrium	**31**	**100%**
Yes	24	77.4%
No	7	22.6%
Left ventricular ejection fraction	**31**	**100%**
< 25%	0	0%
25% – 40%	7	22.5%
> 40%	24	77.42%

5. Antithrombotic therapy and International normalized ratio (INR):

25 patients (80.64%) were under anticoagulants of which 11 patients (44%) had a correct INR and 14 patients (56%) had a labile INR. 1 patient (3.22%) was treated with platelet antiaggregant and 5 patients (16.12%) were not receiving antithrombotic therapy.

Table 5: Antithrombotic therapy of patients

Antithrombotic therapy	Number	Percentage
Anticoagulants	**25**	**80.64%**
Correct INR	11	44%
Labile INR	14	56%
Platelet antiaggregant	**1**	**3.22%**
No antithrombotic therapy	**5**	**16.12%**

6. Brain magnetic resonance imaging (MRI):

12 patients had a normal MRI. 14 patients had territorial cortical infarct (frontal, insular, parietal and cerebellar) and subcortical (semioval centre) lesions. 8 patients had just one lesion (4 in the right and 4 in the left hemisphere). 6 patients had more than one ischaemic areas of which 1 patient had a middle cerebral artery territory infarct and 2 patients had a cerebellar infarct (posterior inferior cerebellar artery territory PICA).

1 patient had a watershed infarct (between anterior cerebral artery and middle cerebral artery territories). 1 patient had a lacunar lesion (basal

ganglia). 2 patients had hemorrhagic lesion (microbleed). 1 patient had both ischaemic and hemorrhagic lesions.

Table 6: Brain MRI lesions of patients

MRI	Number	Percentage
Normal	12	38.7%
Cortical- subcortical infarct	14	45.2%
One ischaemic lesion	8	25.80%
Multiple ischaemic lesions	6	19.40%
Watershed infarct	1	3.2%
Lacunar lesion	1	3.2%
Hemorrhagic lesion	2	6.5%
Both ischemic and hemorrhagic lesions	1	3.5%
Total	31	100%

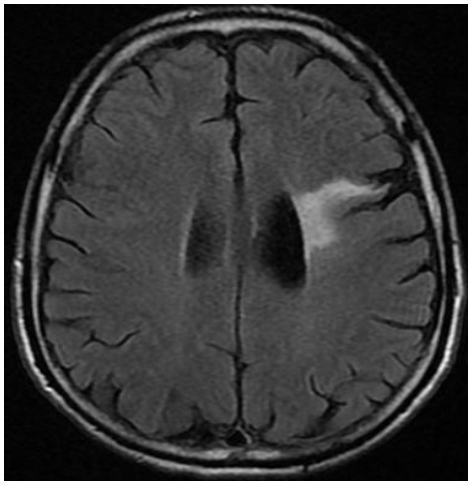

Figure 1: silent infarct in middle cerebral artery territory on brain MRI (FLAIR sequence)

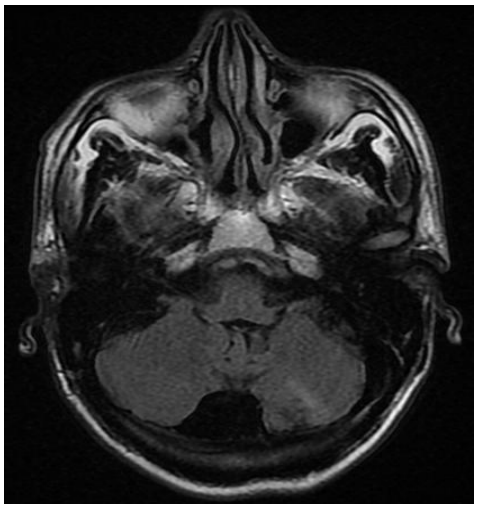

Figure 2: silent infarct in posterior inferior cerebellar artery territory on brain MRI (FLAIR sequence)

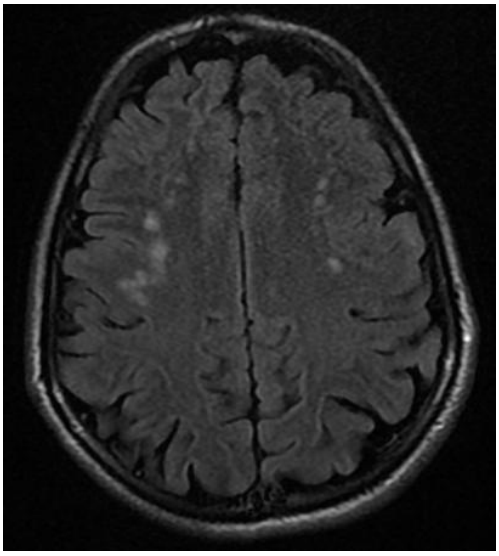

Figure 3: watershed infarct between anterior cerebral artery and middle cerebral artery territories on brain MRI (FLAIR sequence)

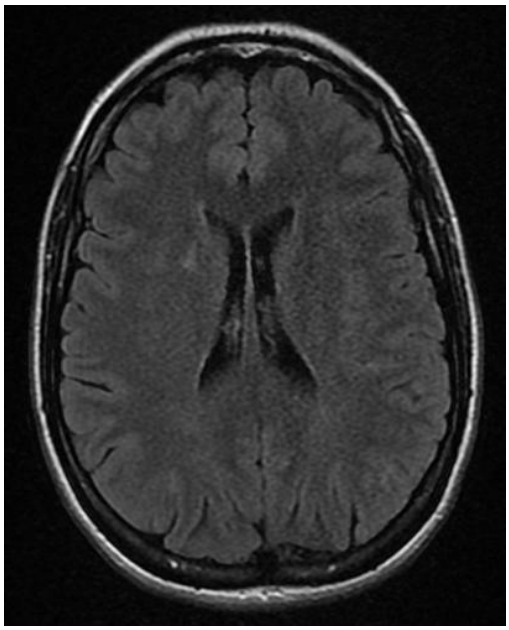

Figure 4: lacunar infarct on brain MRI (FLAIR sequence)

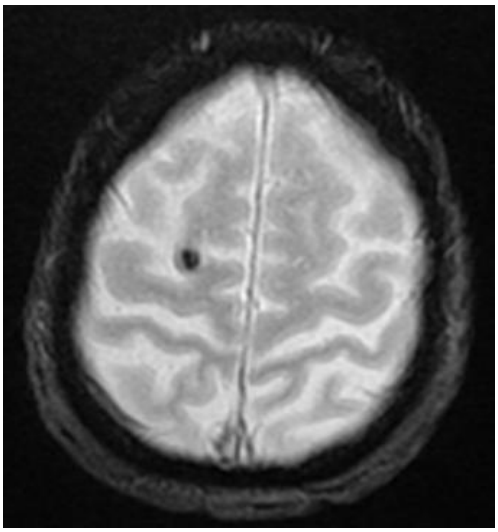

Figure 5: hemorrhagic lesion (microbleed) on brain MRI (T2* weighted sequence)

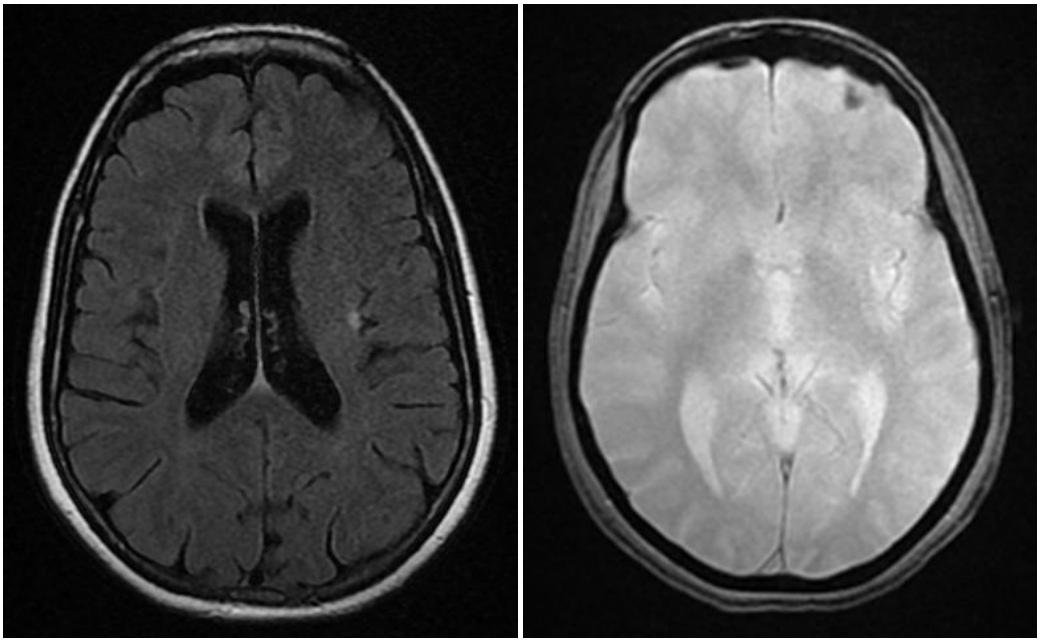

Figure 6: Brain MRI (FLAIR and T2* weighted sequences) of the patient who had both ischaemic and hemorrhagic lesions

7. Results analysis:

No patient had a history of cerebrovascular events (ischemic stroke or transient ischemic attack). Neurological examination was normal in all.

There were no significant differences between the group of patients with normal MRI and the group of patients with ischaemic lesions in age, gender, history of hypertension, diabetes mellitus, hyperlipidemia or smoking.

There was no significant difference in the incidence of silent stroke between patients with an atrial fibrillation and patients with a sinus cardiac rhythm (**p value=1**).

The presence of enlarged left atrium was not statistically associated with the occurrence of silent stroke (**p value=0.201**). Also, the incidence of silent stroke did not differ in patients with more than one valvular disease (**p value=1**).

In the group of patients with silent infarcts, 73.7% of patients had a moderate to severe mitral stenosis, 10.5% of patients had an aortic stenosis and 15.8% of patients had a mitral regurgitation. Mitral stenosis was not statistically associated with silent stroke (**p value=0.944**). This was may be due to the small number of the patients in our series.

There was no significant difference between patients treated with anticoagulants and patients who are not (**p value=1).**

Patients treated with anticoagulants of which the INR was correct had less silent stroke than patients of which the INR was labile (26.7% versus 73.3% respectively). That was statistically significant (**p value=0.049**).

Table 7: Baseline patient's characteristics

Patients characteristics	Normal MRI Number (%)	Silent stroke Number (%)	P value
Age			0.676
≤ 55	10(83.3%)	14(73.7%)	
> 55	2(16.7%)	5(26.3%)	
Male/Female	4(33.3%) /8(66.7%)	8(42.1%) /11(57.9%)	0.717
Hypertension	0(0%)	3(15.8%)	0.216
Diabetes mellitus	1(8.3%)	1(5.3%)	1
Hyperlipidemia	0(0%)	0(0%)	-
Smoking	3(25.0%)	5(26.3%)	1
Atrial fibrillation	9(75.0%)	14(73.3%)	1
Valvular disease			0.944
Moderate mitral stenosis	4(33.3%)	8(42.1%)	
Severe mitral stenosis	5(41.7%)	6(31.6%)	
Mitral regurgitation	2(16.7%)	3(15.8%)	
Aortic stenosis	1(8.3%)	2(10.5%)	
More than one valvulopathy	7(58.3%)	11(57.9%)	1
Enlarged left atrium	11(91.7%)	13(68.4%)	0.201
Anticoagulation therapy			1
Yes	10(83.33%)	15(78.94%)	
No	2(16.67%)	4(21.06%)	
INR			**0.049**
Correct	7(70.0%)	4(26.7%)	
Labile	3(30%)	11(73.3%)	

DISCUSSION

The prevalence of silent stroke in general population detected with brain MRI which is reported in the literature is between 8% and 28% (8).The prevalence of silent stroke increases with age (9-10-11-12-13). It is also reported that females had more silent brain infarcts than males (11- 14). Hypertension is the most risk factor which is strongly associated with silent stroke in several studies (9-15).

Atrial fibrillation is the first cause of cardio-embolic stroke (16). The risk of stroke is five times higher in patients with chronic atrial fibrillation than in patients with sinus rhythm (17-18). Also, there was no difference in increasing risk of stroke between persistent and paroxysmal atrial fibrillation (8). The prevalence and the incidence of atrial fibrillation increases with age and the risk of stroke due to atrial fibrillation rises from 1.5% at the age of 50 to 24% at the age of 80 (19). The association between atrial fibrillation and silent brain infarcts had been widely demonstrated by several studies whether with MRI or CT scan (8-20-21-22-23-24-25-26).

Rheumatic heart disease affects between 15 and 20 million people worldwide of which the most of them are children and young adults living in developing countries (27). The most common etiology of mitral stenosis is the rheumatic heart disease. In Morocco, the prevalence of rheumatic heart disease is 0.3 to 1%. It is responsible for 10% of hospitalizations in medical departments and more than 50% in cardiology departments (28). Mitral stenosis becomes more severe when it is complicated by atrial fibrillation. It affects approximately 40% of patients with mitral stenosis and predisposes these patients to a thromboembolic event (29). The risk of stroke is twenty

times higher if the etiology of atrial fibrillation was a rheumatic valvular heart disease (17-18).

The first study that explored silent stroke in patients with rheumatic mitral stenosis was made by Akdemir et al from cardiology department of university of Gaziantep in Turkey using computed tomography (CT) scan images (20). The incidence of silent stroke in this study was 24.5%. They suggested that the rate could be higher if they used MRI instead of CT scan.

In our study, the prevalence of silent stroke was 54.83%. The majority of our patients had 3 predominant echographic features: moderate to severe mitral stenosis, enlarged left atrium and more than one valvulopathy. 73.7% of patients with silent stroke had a moderate to severe mitral stenosis (42.1% and 31.6% respectively). 68.4% of patients with silent stroke had an enlarged left atrium. 57.9% of patients had more than one valvulopathy (mitral or tricuspid regurgitation were associated to the mitral stenosis). These three echographic features were not statistically significant between patients with or without silent infarcts. It is probably due to the small size of our series. However, in the Turkish series (53 patients), the enlarged left atrium was statistically associated with increased risk of silent stroke (20). Also, the incidence of silent stroke was higher in patients with moderate to severe mitral stenosis without statistical significance (20).

73.3% of our patients with silent stroke had atrial fibrillation but it was not statistically significant between patients with or without silent infarcts. In the Turkish study, atrial fibrillation was associated with high risk of silent

stroke (p value<0.005). Also, the study demonstrated that the coexistence of enlarged left atrium and atrial fibrillation increases even more the risk of silent stroke in patients with mitral stenosis (20).

MRI seems to be more sensitive than CT scan in detecting silent infarctions.

Table 8: Prevalence of silent stroke in patients with atrial fibrillation (20-21-22-23-24-25-26)

Study	Country	Imaging	Atrial fibrillation (N)	Type of atrial fibrillation (AF)	Silent stroke (N)	Percentage (%)
Petersen et al (21)	Denmark	CT scan	29	Non valvular AF	14	48%
Guidotti et al (22)	Italy	CT scan	72	Non valvular AF	32	44%
Zito et al (23)	Italy	Ct scan	38	Non valvular AF	16	42%
Kobayashi et al (24)	Japan	MRI	71	Non valvular AF	35	49%
Marfella et al (25)	Italy	MRI	176	Non valvular AF	107	61%
Saito et al (26)	Japan	MRI	131	Non valvular AF	42	32%
AKDEMIR et al (20)	Turkey	CT scan	25	Valvular AF	10	40%
Our Study	**Morocco**	**MRI**	**23**	**Valvular AF**	**14**	**73%**

In our series, 8 patients had sinus rhythm of which 5 of them (62.5%) had silent infarctions. We can suggest that rheumatic valve heart disease even without atrial fibrillation is associated with an increased risk of silent cerebral cardioembolism. In the literature, rheumatic valvular heart disease in particular mitral stenosis and calcific aortic stenosis is a risk factor for stroke even without atrial fibrillation (30).

One of our patients had a lacunar infarct (right caudate nucleus). Lacunar infarcts are small deep cerebral infarctions in the basal ganglia (caudate, lenticular nucleus, thalamus), internal capsule or brainstem (pons). They are the result of the occlusion of small penetrating cerebral arteries often associated with hypertension (31). It was demonstrated that microemboli can obstruct deep penetrating cerebral arteries and causing cardioembolic lacunar infarcts (32). Tuszynski et al found some cardiac sources of embolism in patients with lacunar infarctions as well as rheumatic valvular heart disease associated with atrial fibrillation in the absence of hypertension or other disease of perforating arteries (33). These findings allowed to retain cardioembolism as a rare cause of lacunar infarcts. For our patient, she was young with no history of hypertension. She had a severe mitral stenosis with enlarged left atrium and atrial fibrillation. The presence of these several risk factors suggests the probability of the cardioembolic source of this lacunar infarct.

One of our patients had a watershed infarct between anterior cerebral artery and middle cerebral artery territories. He had sinus rhythm, aortic stenosis with left ventricular ejection fraction at 50%. He had no history of hypotension. This heart condition could be responsible of low cerebral perfusion and therefore caused this watershed infarct. However, an ultrasonography of internal carotid arteries should be performed to eliminate an occlusion which is another source of embolism that can be the cause of the infarct. That was one of the limitations of our study.

78.94% of our patients with silent stroke were already under anticoagulation therapy. 73.3% of these patients had labile INR. That was statistically significant (P value<0.05) between patients with and without silent infarcts. Six patients were not treated with anticoagulants of which 4 of them (66.66%) had silent infarcts but it was not statistically significant because of the low number of this group. These findings suggest that effective anticoagulation therapy plays a major role in preventing silent stroke in patients with rheumatic valvular heart disease with or without atrial fibrillation. In fact, risk factors of cardioembolism in rheumatic valvular heart disease include atrial fibrillation, enlarged left atrium and metallic prosthetic valves (34). Also, it was reported that patients with mitral stenosis had probably a left atrial appendage dysfunction (35) which lead to thrombus formation that have cerebral tropism increasing therefore the risk of silent stroke (20). That's why; anticoagulation therapy could be indicated in patients with rheumatic valvular heart disease if they have other risk factors of thromboembolism apart from atrial fibrillation. That was the case of 2 of our patients who had sinus rhythm but they were treated with anticoagulants because of the presence of a severe mitral stenosis with enlarged left atrium.

Many patients can not have a regular INR monitoring in developing countries because of the economic level of patients or the absence of laboratories which increase the risk of thromboembolism or on the contrary the risk of bleeding.

The silent character of these brain infarcts is very probably due to the small size and location in silent brain areas or to their production of a minor deficit that may have gone unreported and unrecognized as symptomatic

stroke (1). It was reported in some studies that patients with silent stroke were presenting in the neurological examination limb weakness, visual field amputation (10-14), depression and cognitive decline (36-37). Silent stroke was associated with twofold increased risk of dementia (9-36). A neuropsychological test could objectify some cognitive abnormalities unnoticed by patients with silent brain infarctions (22).

In the literature, silent stroke is associated with an increase risk of transient ischemic attack and minor stroke (9-38). Also, elderly people with silent infarcts had three times increased risk of symptomatic stroke in general population independently of the others risk factors (39).

These findings prove that patients with silent stroke are at high risk to develop a symptomatic stroke in the future. That is why these patients require a serious therapeutic management.

The challenges are may be the good management of all the cardiovascular risk factors which are reported in our study before the occurrence of silent stroke.

In our context, the treatment of repeated episodes of angina in childhood could significantly reduce the incidence of rheumatic valvular heart disease (primary prevention). The early surgical management (valvular replacement) before the stage of cardiac complications and the raising awareness of therapeutic compliance essentially anticoagulation therapy could also significantly reduce the incidence of silent stroke.

CONCLUSION

Rheumatic valvular heart disease is a major cause of cerebral cardioembolism. Our study had documented the relation between this frequent heart disease in our context and silent stroke. In fact, patients with moderate to severe mitral stenosis are at a high risk of silent stroke. The coexistence of atrial fibrillation and enlarged left atrium increases the risk of silent stroke.

We also demonstrated that anticoagulation therapy had a major role to reduce de risk of silent stroke. This category of patients should be considered at a high risk of occurrence of a symptomatic stroke and should have a serious therapeutic management to all their risk factors to avoid heavy consequences.

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