Bayés syndrome and acute cardioembolic ischemic stroke

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Bayés syndrome is an under-recognized clinical condition characterized by advanced interatrial block. Bayés syndrome is a subclinical disease that manifests electrocardiographically as a prolonged P wave duration > 120 ms with biphasic morphology ± in the inferior leads. The clinical relevance of Bayés syndrome lies in the fact that is a clear arrhythmological syndrome and has a strong association with supraventricular arrhythmias, particularly atypical atrial flutter and atrial fibrillation. Likewise, Bayés syndrome has been recently identified as a novel risk factor for non-lacunar cardioembolic ischemic stroke and vascular dementia. Advanced interatrial block can be a risk for embolic stroke due to its known sequelae of left atrial dilation, left atrial electromechanical dysfunction or atrial tachyarrhythmia (paroxysmal or persistent atrial fibrillation), conditions predisposing to thromboembolism. Bayés syndrome may be responsible for some of the unexplained ischemic strokes and shall be considered and investigated as a possible cause for cryptogenetic stroke. In summary, Bayés syndrome is a poorly recognized cardiac rhythm disorder with important cardiologic and neurologic implications.

Key words: Bayés syndrome; Cardioembolic stroke; Electrophysiological processes; Cardiovascular risk factors; Heart conduction system

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CONCEPT AND DEFINITIONS

preventive therapies. possibly accompanying antiarrhythmic and antithrombotic since patients will require closer clinical surveillance, and diagnosis of Bayés syndrome is desirable and necessary, is a key independent factor of cardioembolic cerebral symptom free at discharge are less frequent (14.3% higher in-hospital mortality (21.9% compared to other subtypes of cerebral infarction with patients with cardioembolic cerebral infarction is poorer banks of Catalonia and Spain, the short prognosis of registry (Table 1), which is one of the first stroke data life expectancy represent the majority of elderly people due to their higher more frequent in men, may also be related to increasing in women compared to non cardioembolic, which are with age was found, with a prevalence of atrial fibrillation with age. In the Framingham study, a growing may be explained by the increasing prevalence of atrial fibrillation with age. In the Framingham study, a growing population attributable risk of stroke due to atrial fibrillation with age was found, with a prevalence of atrial fibrillation of 1.8% in patients aged 60-69 years, 4.8% in those aged 70-79 years, and 8.8% in the 80 to 90 year group. Similarly, the increased frequency of cardioembolic infarcts in women compared to non cardioembolic, which are more frequent in men, may also be related to increasing age observed in the industrialized societies, where women represent the majority of elderly people due to their higher life expectancy.

In the Sagrat Cor Hospital of Barcelona Stroke Registry (Table 1), which is one of the first stroke data banks of Catalonia and Spain, the short prognosis of patients with cardioembolic cerebral infarction is poorer compared to other subtypes of cerebral infarction with higher in-hospital mortality (21.9% vs 8.2%), whereas symptom free at discharge are less frequent (14.3% vs 19.9%).

Recent studies have shown that Bayés syndrome is a key independent factor of cardioembolic cerebral ischemia[1,2], although there is still a need of high level of clinical suspicion in order to diagnose it. Early and proper diagnosis of Bayés syndrome is desirable and necessary, since patients will require closer clinical surveillance, and possibly accompanying arrhythmic and antithrombotic preventive therapies.

CONCEPT AND DEFINITIONS

In analogy to other cardiac conduction delays, atrial conduction abnormalities should be divided into partial and advanced interatrial blocks (aIAB) or Bayés syndrome. The syndrome of advanced interatrial conduction block due to conduction impairment in Bachmann’s bundle, results in delayed and retrograde activation of the left atrium that signifies a conduction delay between the left and right atria, and it is associated with a high incidence of atrial tachyarrhythmias, especially a particular and specific form of atypical atrial flutter or atrial fibrillation[11,12].

The first case of inter-atrial block was described by Bachmann[13] in 1941. Later, in 1971, Castillo and Vernant[14] emphasized that when a P wave with plus/min (biphasic) morphology is observed in leads II, III, and aVF, the atrial stimulus is blocked in the upper part of the septum. Finally, between 1979 and 1985, Bayes de Luna et al[15,16] precisely analyzed the prevalence, pathological associations, and profile of the arrhythmias associated with aIAB, thereby defining a distinct and well-defined anatomico-electrical entity. Dr. Bayés de Luna contribution was fundamental in demonstrating the association between advanced interatrial block and supraventricular arrhythmias, thus confirming a well-defined arrhythmical syndrome. The consensus of naming this association with the eponymous Bayés syndrome has recently been accepted by the scientific community in honor of Dr. Antoni Bayés de Luna, the great Catalan master of clinical electrocardiography[17,18], for his contribution to the understanding of the natural history of this cardiac syndrome. However, Bayés syndrome remains an under-recognized clinical condition.

Bayés de Luna described the electrocardiographic pattern for identifying IAB and classified the types of block that occur at the atrial level. The distinction is based on the P-wave duration, and more important, the P-wave morphology: A partial block, indicated by a P-wave plus/min morphology is observed in leads II, III, and aVF (Figure 1). If the interatrial block is advanced, also, the P wave is prolonged (duration 120 ms or more), but the second part of the P wave in inferior leads becomes negative (biphasic pattern or P-wave plus/min morphology) because of the retrograde activation of the left atrium (P-wave ≥ in II, III, and aVF) (Figure 2)[19-21].

It should be noted that, initially, IAB may occur
transiently and may be reversible. It may be classified as first-degree (partial), second-degree (transient interatrial block or atrial aberrancy), or third-degree (advanced). There is consensus on considering transient interatrial block as a marker of electromechanical dysfunction of the left atrium and a risk factor for recurrence of atrial fibrillation [11,15].

Although the diagnosis of interatrial block is frequently associated with left atrial enlargement (LAE), there are some cases, especially of first-degree IAB, without this association. Therefore, it should be noted that IAB is a separate entity from atrial enlargement [11,22].

The prevalence of interatrial block is age-dependent, increasing from 5.4% at < 20 years old to 60% at > 50; in the same way, advanced IAB increases from 0.1% to 2% in patients with heart valve disease and cardiomyopathy [23,24]. The increased age-related risk may be probably due to atrial fibrosis which would result in impaired atrioventricular conduction through the atria. However, the exact pathogenesis has not been elucidated and various comorbidities, including coronary heart disease, arterial hypertension, and diabetes mellitus, have been proposed. The cause of IAB may be likely degenerative because of the increased incidence with age [11].

ASSOCIATION OF INTERATRIAL BLOCK WITH SUPRAVENTRICULAR ARRHYTHMIAS

The Bayés syndrome is a clear arrhythmological syn-
Table 2 Main studies of interatrial block as a cerebrovascular risk factor or as a predictor for acute ischemic stroke (period 1979-2016)

| Ref.          | Study type       | n      | Age (yr) | Gender | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Parameters evaluated                      | Results                                                                 |
|--------------|------------------|--------|----------|--------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------------------------------|------------------------------------------------------------------------|
| Wu et al[32] | Retrospective    | 1046   | 63 ± 10  | 612 males, 434 females                                                                 | Patients hospitalized in Zhengzhou University People’s Hospital for diagnosis and treatment between March 1 and March 31 of 2010 | Conduction lengths, CHADS2 and CHA2DS2-VASc scores                               | Mean follow-up of 4.9 ± 0.7 yr, 0.8% hemorrhagic stroke, 5.3% presented ischemic stroke or TIA, increased with CHADS2 score: 0.37, 0.85, 0.96 and 1.92 per 100-person years for scores of 0, 1, 2, and > 3 respectively, CHA2DS2-VASc scores correlated with ischemic stroke or TIA (0.19, 0.59, 0.76, 0.88, and 2.0 for scores of 0, 1, 2, 3, and > 4 respectively), Cut-off points: > 3 for CHADS2, > 4 for CHA2DS2-VASc. Conclusion: CHADS2 and CHA2DS2-VASc scores may be predictors of risk of ischemic stroke or TIA in patients with IAB without atrial fibrillation. Advanced IAB is a pre-atrial fibrillation condition associated with premature atrial beats. Atrial arrhythmias and IAB occurred more frequently in centenarians than in septuagenarians. Incidence rate of ischemic stroke was higher in aIAB (8.05/1000 person-years vs 3.14; P < 0.0001). Conclusion: aIAB was associated with incident ischemic stroke. |
| Martinez-Selles et al[44] | Case-control | 80     | 101.4 ± 1.5 | 21 males, 59 females                                                                  | Patients from the Cardiac and Clinical Characterization of Centenarians (4C) Registry | Conduction lengths, ECG measurements, Short Portable Mental Status Questionnaire, Premature atrial beats | IAB group showed higher rate of previous stroke than normal P-wave and AF groups. Premature atrial beats were more frequent in advanced IAB than normal P-wave. Mitral regurgitation could play an important role in IAB. Conclusion: Advanced IAB is a pre-atrial fibrillation condition associated with premature atrial beats. Atrial arrhythmias and IAB occurred more frequently in centenarians than in septuagenarians. Incidence rate of ischemic stroke was higher in aIAB (8.05/1000 person-years vs 3.14; P < 0.0001). Conclusion: aIAB was associated with incident ischemic stroke. |
| O’Neal et al[24] | Retrospective     | 14716  | 54 ± 5.8  | 6622 males, 8094 females                                                               | Patients enrolled in the ARIC Study Recruited between 1987 and 1989 | Conduction lengths, Presence of stroke Type 3 Stroke | Incidence rate of ischemic stroke was higher in aIAB (8.05/1000 person-years vs 3.14; P < 0.0001). Conclusion: aIAB was associated with incident ischemic stroke. | |

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| Study | Design | N | Age Range | Gender | Key Findings |
|-------|--------|---|-----------|--------|--------------|
| O'Neal et al. [29] | Retrospective cohort | 14025 | 54 ± 5.8 | 6581 males, 8044 females | Participants enrolled in the ARIC Study Recruited between 1987 and 1989. Participants with AF at baseline. Missing baseline covariates. Missing follow-up data. Age other than black or white. Black participants from Washington County and Minneapolis. Conduction lengths. | Total of 262 aIAB patients (69 baseline, 193 new). 1929 AF cases were identified. aIAB patients presented an AF incidence of 29.8/1000 vs 6.8/1000 of non-aIAB; HR = 3.09 (P < 0.0001). Conclusion: aIAB is a useful marker to identify high-risk subjects for developing atrial fibrillation. |
| Pirinen et al. [41] | Case-control | 690 | 15-49 | 438 males, 252 females | Correct diagnosis of IS Part of the Helsinki Young Stroke Study. Unknown stroke date. Outpatient treatment only. No ECG OR only take on the day of stroke in ER OR no ECG between day of stroke and 14 d after. Conduction lengths. | Most Common ECG abnormalities: T-wave inversion (LVH (14%), prolonged P-wave (13%), prolonged QTc (12%). Most ECG abnormalities in the Stroke Etiology Subgroups: HRCE, LAA and SVD. Conclusion: Routine ECG provides useful information for directing the work-up of a young IS patient. In addition to AF, P-terminal force in particular showed a strong association with etiology of high-risk source of cardioembolism. |
| Enriquez et al. [42] | Prospective cohort | 187 | 67 ± 10.7 | Not reported | Patients with typical atrial flutter (AF) with no prior history of AF referred for CTI ablation. Patients that had received repeat ablations or did not demonstrate a bidirectional block. Composite of Cardiovascular Disease not reported. | Advanced IAB was detected in 18.2% of patients. Left atrium was larger in aIAB (46.2 ± 5.9 mm vs 43.1 ± 6.0 mm; P = 0.01). 35.8% of patients developed new-onset AF. Mean AF duration was 6 min. Conclusion: In patients with unexplained stroke atrial fibrillation was detected by implantable loop recorders in 25.5%. IAB was an independent predictor of AF. |
| Cotter et al. [30] | Retrospective cohort | 51 | 17-73 | 28 males, 23 females | ILR implanted after unexplained ischemic stroke. Brain imaging consistent with embolism. Arterial imaging. Structural cardiac imaging and rhythm monitoring 50 d of continuous monitoring. | Conduction lengths. | 25.5% of cases had AF. IAB more prevalent in patients with AF (P = 0.02). AF patients larger LA volumes (P = 0.025). Mean AF duration was 6 min. Conclusion: In patients with unexplained stroke atrial fibrillation was detected by implantable loop recorders in 25.5%. IAB was an independent predictor of AF. |
| Cotter et al. [31] | Case-control | 78 | 24-55 | ≤ ≤ 55 yr at time of stroke | Poor quality data. | Rhythm monitoring. | Mean AF duration was 6 min. Conclusion: In patients with unexplained stroke atrial fibrillation was detected by implantable loop recorders in 25.5%. IAB was an independent predictor of AF. |
| Study | Type | Number | Age Range | Sex | Diagnosis |
|-------|------|--------|-----------|-----|-----------|
| Ariyarajah et al.⁴³ | Case-control | 66 | 60-87 | 39 males, 27 females | Definitive acute or subacute cerebral infarct, Probable embolic origin, No 12-lead ECG during 14 d post infarct, Non-sinusual rhythm detected in ECG | Hypertension, Valvulopathies, Cardiomyopathies, Tobacco Use, Dyslipidemia, Diabetes Mellitus, Hyper/hypothyroidism, COPD, Flord Heart Failure, Cardiac Catheterization, Myocardial Infection, Valvuloplasty, Previous strokes/TIA, History of AF/Flutter, CAD |
| Ariyarajah et al.⁴⁵ | Case-control | 228 | 30-102 | 118 males, 110 females | Studied for suspicion of stroke with CT Scan and MRI, No 12-lead ECG during 14 d post infarct | Hypertension, Valvulopathies, Cardiomyopathies, Tobacco Use, Dyslipidemia, Diabetes Mellitus, Hyper/hypothyroidism, COPD, Flord Heart Failure, Cardiac Catheterization, Myocardial Infection, Valvuloplasty, Previous strokes/TIA, History of AF/Flutter, CAD |
| Ariyarajah et al.⁴⁶ | Prospective cohort | 32 | 66-94 | 15 males, 17 females | Not reported | Mitral or tricuspid valvar disease, Hypertension, Coronary artery disease, Hyperlipidemia, Diabetes mellitus, History of AF/Flutter, ACEI use, Beta-blocker use, Statins use | Conduction lengths, Stroke etiology |

No statistical difference of P-wave length (with vs without PFO)

Conclusion: In young patients with unexplained stroke, particularly those with patent foramen ovale atria l dysfunction is a possible mechanism of stroke

61% IAB prevalence CAD paroxistically more present in control, perhaps due to atherosclerotic origin LA more prevalent in IAB group, with greater LA thrombi (83% vs 0%)

Conclusion: IAB could be a risk factor for embolic stroke due to its known sequelae of left atrial dilation and electromechanical dysfunction that predispose to thrombosis

61% IAB embolic vs 40% non-embolic (P = 0.006)

Hypertension for embolic stroke (P < 0.0001)

Conclusion: IAB could be a novel risk for embolic stroke

Coronary disease was more prevalent in the IAB group

Cardiovascular events were overall most significant in IAB, except for stroke, TIA, peripheral arterial embolism and atrial flutter

Conclusion: In patients with comparable echocardiographic parameters, IAB remained associated with atrial fibrillation after 15-mo follow-up
drome. Advanced IAB is a key predictor for high risk of new-onset atrial fibrillation after a successful cavo-tricuspid isthmus ablation in patients with typical atrial flutter\[11,25\].

A clinical study reported that 90% of patients with atrial fibrillation recurrence at one year had advanced IAB, and multivariate analysis demonstrated that persistent IAB was a predictor of AF recurrence. Advanced IAB is a useful marker to identify subjects who are at high risk for developing atrial fibrillation, and is a pre-atrial fibrillation condition associated with premature atrial beats\[24\].

Practical consequences and clinical implications of Bayés syndrome are the high incidence of atrial extrasytoles and paroxysmal supraventricular tachyarrhythmia, especially in patients with valvular heart disease or cardiomyopathy. A control group of patients with similar clinical states and left atrial size by echocardiography showed much lower incidence of these arrhythmias\[11\]. Bayés de Luna et al\[26\] also suggested that antiarrhythmic treatment prevents recurrences of atrial tachyarrhythmia in these cases.

There are currently no evidence-based recommendations on the most appropriate therapeutic approach for Bayés syndrome in any of the different cardiologic or neurologic guidelines for primary or secondary prevention of cerebral ischemia. A clinical case of a patient with Bayés syndrome reported antiarrhythmic treatment with amiodarone and anticoagulant administration with acenocoumarol\[27\].

Prolonged QRS duration is an independent predictor of cardiovascular mortality in patients with underlying structural heart disease. Similarly, the relation between sudden death and QT prolongation is an established fact\[11\]. Increased P wave duration is the only P wave index significantly associated with increased cardiovascular mortality. Therefore, IAB as a subclinical disease merits elucidation as a marker of risk for adverse outcomes.

### A NEW RISK FACTOR FOR CEREBRAL INFARCT AND VASCULAR DEMENTIA

Recently, Bayés syndrome has been shown to be a predictor of cardioembolic stroke\[28\]. There are three main consequences of advanced IAB: Firstly, IAB is a substrate for sustained AF, and the association between AF and advanced IAB has been demonstrated. Secondly, IAB results in poor left atrium (LA) contractility due to a delayed depolarization which can result in LA dysfunction. Such a delay has hemodynamic consequences including raised LA pressure and LA dilatation, which again is a substrate for AF. Thirdly, IAB may be associated with structural factors as a result of left atrium enlargement, although it may occur in patients with normal left atrium size\[11\].

As a result, advanced IAB could be a risk for embolic stroke due to its known sequelae of left atrial dilation, LA electromechanical dysfunction or atrial tachyarrhythmias, conditions which predispose to the formation of echo-contrast, and may serve as a nidus for thrombi or microthrombi, and thus increase the risk for cardioembolic events. Because IAB predicts atrial fibrillation, patients with IAB may intermittently be in atrial fibrillation (paroxysmal atrial fibrillation), causing embolization\[11\].

Ariyarajah et al\[27\] analyzed 293 patients with cerebral
infarct, 85 of them cardioembolic, and reported that 88% of cardioembolic infarcts showed sinus rhythm and 61% of these had advanced IAB, concluding that IAB could be a novel risk factor for embolic stroke.

In an analysis of ARIC (Atherosclerosis risk in Communities Study) advanced IAB was independently associated with an increased risk for ischemic stroke, thus definitively confirming IAB as a novel risk factor for cardioembolic ischemic stroke. Cotter et al reported an increased incidence of interatrial block in younger adults with cryptogenic stroke and patent foramen ovale, suggesting atrial arrhythmias as a possible cause of unexplained ischemic stroke in these patients. In another study, atrial fibrillation detected by implantable loop recorders in unexplained stroke was identified in 25.5% of cases, and AF was independently associated with interatrial conduction block. In a clinical study the CHADS2 and CHADS2-VASc scores could predict the risk of ischemic stroke or TIA in patients with IAB without atrial fibrillation. However, the association of Bayés syndrome and ischemic stroke is limited to non-lacunar cardioembolic infarcts. Lacunar infarcts are an ischemic stroke subtype related mainly to hypertension and diabetes. Ischemic stroke of unusual causes accounted for 5% of ischemic strokes and the association of advanced IAB in this ischemic stroke subtype is improbable.

By contrast, it is important to highlight that about 10%-30% of ischemic strokes remain cryptogenic despite reasonably thorough evaluations. A possible explanation for this is that IAB may be responsible for some of the unexplained strokes.

FUTURE RESEARCH

Recognition of Bayés syndrome is not merely an academic issue. It allows selecting high-risk patients for which pharmacological therapy could be beneficial. Open questions remain to be addressed with well-designed clinical trials including whether antiarrhythmic and/or anticoagulant drugs could be used in patients with advanced IAB without atrial tachyarrrhythms to prevent both AF and embolic stroke.

Additional epidemiological studies would be needed to define the possible connection between Bayés syndrome and clinically silent cerebral infarctions, small vessel disease, cognitive impairment of vascular type or dementia.

CONCLUSION

Bayés syndrome is a poorly recognized cardiac rhythm disorder with important clinical implications. Bayés syndrome is a pre-atrial fibrillation condition and should be considered a novel and important risk factor for cardioembolic stroke and vascular cognitive impairment.

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