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End-of-term project

THE UTILITY OF IMPLANTABLE LOOP RECORDER IN THE CLINICAL MANAGEMENT OF PEDIATRIC PATIENTS WITH NON-HIGH-RISK BRUGADA SYNDROME

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A la meva família, per tots aquests anys de recolzament constant i per acompanyar-me pel camí que tot just acaba de començar. Donar gràcies als meus germans, per ser un pilar fonamental.

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"Un viatge de mil milles, comença amb un pas" – Laozi

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1. LIST OF ABBREVIATIONS

ADD	Antiarrhythmic drugs
AP	Action potential
AV	Atrio-ventricular
BrP	Brugada pattern
BrS	Brugada syndrome
ECG	Electrocardiogram
EPS	Electrophysiological study
ICD	Implantable cardioverter defibrillator
ILR	Implatable loop recorder
NSVT	Non-sustained ventricular tachycardia
RBBB	Right bundle branch block
RVOT	Right ventricular outflow tract
SCD	Sudden cardiac death
SD	Sudden death
VF	Ventricular fibrillation
VT	Ventricular tachycardia

2. ABSTRACT

BACKGROUND: Brugada syndrome (BrS) is an inherited arrhythmogenic disorder characterized by a typical ECG pattern. The syndrome has incomplete penetrance and variable expressivity, ranging from asymptomatic to lethal ventricular arrhythmias and sudden death at a young age in individuals with structurally normal hearts. So, all this requires an early diagnosis and an accurate risk stratification of this population.

HYPOTHESIS AND OBJECTIVE: We suggest the use of remote monitoring system using a subcutaneous loop recorder as a tool to detect arrhythmic events that can help in the risk stratification of pediatric patients with non-high-risk BrS.

METHODS AND MATERIALS: A retrospective cohort study was performed to describe data collected by implantable loop recorder (ILR) of 34 anonymized pediatric patients with non-high-risk BrS. Their demographic and clinical characteristics and the results obtained in all diagnostic tests performed, were analyzed in comparison to the detection of arrhythmic events by ILR.

RESULTS: Within 34 patients, 24 were male (70,59%) and 10 were female (29,41%). Among total arrhythmic events detected, 5 patients (45,45%) were previously symptomatic and 6 (54,55%) were previously asymptomatic. During a mean follow-up of 18 months, a total of 7 cases (63,64%), ILR was triggered by symptoms, which in the majority of them (71,43%) were proved normal sinus rhythm/sinus tachycardia or minimal rhythm disturbances. In the two remaining symptomatic cases (28,57%), the ECG tracing identified episodes of NSVT. That involved a change in those patients' therapeutic management, requiring an early implantation of ICD. In four asymptomatic patients (36,36%) the ILR recording was auto-activated, showing in one of those cases (25%), various episodes of asymptomatic NSVT. In six cases (17,65%), ILR recorded episodes of abrupt change repolarization compatible with dynamic BrS.

CONCLUSIONS: The ILR was determinant to exclude ventricular arrhythmias as a mechanism of symptoms in 71,43% of patients, delaying ICD implantation. In contrast, it allowed to detect ventricular arrhythmias in two symptomatic patients, leading to an early implantation of ICD. So, the ILR allows a long-term continue monitoring of heart rhythm in patients with increased risk of suffering life-threatening arrhythmias and should be considered as a tool for clinical management of paediatric patients with non-high-risk BrS

KEYWORDS: Brugada syndrome, children, arrhythmia, sudden cardiac death, implantable loop recorder.

3. INTRODUCTION

3.1 Definition of Brugada Syndrome

Sudden cardiac death (SCD) is defined as an unexpected cardiac function cessation in apparently healthy individuals which accounts for nearly 85% of all sudden death (SD). Most of cases of SCD in patients over 40 years old are the result of coronary heart disease. In contrast, in the young-adult population (<35 years old) SCD is often caused by arrhythmic syndromes with or without structural heart alterations called cardiomyopathies and channelopathies respectively. Channelopathies are a group of familial arrhythmogenic syndromes caused by pathogenic alteration in genes encoding ion channels or associated proteins, which participate in cardiac cell action potential (AP), group from which the Brugada syndrome (BrS) belongs. This syndrome can apparently predispose healthy individuals to suffer from malignant cardiac arrhythmia or ultimately to develop SCD.

Despite its life-threatening nature, most patients remain completely asymptomatic and undiagnosed, but they have potential risk of SCD, leading to an important medical challenge.

3.2 Brugada syndrome history [1-3,8,33]

The syndrome of “Right Bundle Branch Block, Persistent ST Segment Elevation and Sudden Cardiac Death”, better known nowadays as Brugada Syndrome was first described in November 1992 by two cardiologists Pedro and Josep Brugada as a new clinical-electrocardiographic syndrome causing ventricular arrhythmias and SCD in patients with a structurally normal heart[1]. A year later, many countries found out that this could be the same disease as what they called “Sudden Unexplained Nocturnal Death Syndrome” (SUNDS) or with different colloquial names such as Bangungut in Philippines, Pokkuri in Japan or Lai tai in Thailand, places where BrS is more prevalent.

After its initial description, which included eight individuals, the documentation of new isolated cases continued always within family nuclei so a genetic bases was suspected. In 1998, Ramon Brugada’s research identified the first genetic mutation related with BrS, confirming that it was a real new syndrome and it could be genetically determined. From that moment, numerous studios were published

focused on trying to define better from its epidemiology, clinical and diagnostic characteristics to its therapeutic managements, in all groups of age. After all these years of scientific progress, there is still a long way to go, looking for new improvements regarding the many facets of BrS that remain still unknown.

3.3 Introduction to pediatric BrS

In the original description, three out of eight patients were children affected by malignant arrhythmias[1]. Since then, several isolated cases have been reported, but data of BrS in pediatric population remains limited.

The prevalence of BrS in pediatric population is lower than in adult population[5,16] and lacks of male predominance, which is clearly defined in adult population, despite equal genetic transmission of the defective gene, possibly because of the low levels of testosterone found in children of both genders[8,9,33] and its role on phenotype expression. In consequence, the hormonal changes which take place in puberty could explain why the risk of spontaneous arrhythmias increase after puberty only in male[15,54,55], when testosterone rises up, although females are not spared from it[8]. Testosterone acts increasing the potassium currents, a key ion involved in triggering ventricular arrhythmias. Surprisingly, most males develop arrhythmias with a mean age of 41$\pm$15 years[13,17,20] rather than shortly after puberty, which means that additional proarrhythmic factors must come into play during adulthood[7,15].

3.4 Epidemiology of BrS

Brugada syndrome is more common among adult men, where represents the 80% of all patients[17,56-58], with an estimated prevalence of 0.14-0.7% in adult population and much lower in children, around 0.0098%[16,24], even though in countries where this disease is endemic it could be increased[24,33,38]. BrS is responsible for 4%-12% of all SD and up to 20% of SD in patients with structurally normal hearts[5,9,13]. Geographical variability has been observed, being more frequent in certain regions of Southeast Asian[9].

3.5 Etiology and physiopathology of BrS

The BrS has a multifactorial etiology including genetics, hormones and environmental components that modifies its phenotype[7]. In the healthy heart, myocardial AP is generated by ionic changes across the membrane: inward currents of Na^+ and Ca^{2+} causing depolarization and outward currents of K^+ enabling repolarization. Modifications in such AP is due to pathogenic variants in genes encoding ion channels or associated proteins predispose to potentially malignant arrhythmias. The first genetic alteration associated with BrS was identified in the SCN5A gene[5] which encodes the α-subunit of the cardiac sodium channel, Nav 1.5 (a transmembrane protein that mediates the fast influx of Na^+ ions generating the initial upstroke of the AP and enabling its propagation in the excitable cardiac tissue)[19]. In BrS, SCN5A mutation leads to a loss-of-function phenotype[4] that manifests as a cardiac conduction disease. That mutation reduces the inward sodium channel current disrupting the delicate ion balance of the cardiac cell. Its impact it is larger in the epicardium compared to the endocardium and myocardium due to the greater expression of the channel carrying the transient outward potassium current (I_{to}), related with repolarization, in epicardium. In consequence, it creates a transmural (epicardial-to-endocardial) voltage gradient, more prominent at the base of the right ventricle, leading to mark heterogeneity in repolarization, responsible for the ST-elevation in the ECG. Finally, that heterogeneity allows a local re-excitation (referred to as "phase 2 reentry"), resulting in ventricular extrasystoles which may trigger episodes of VT/VF[18,19].

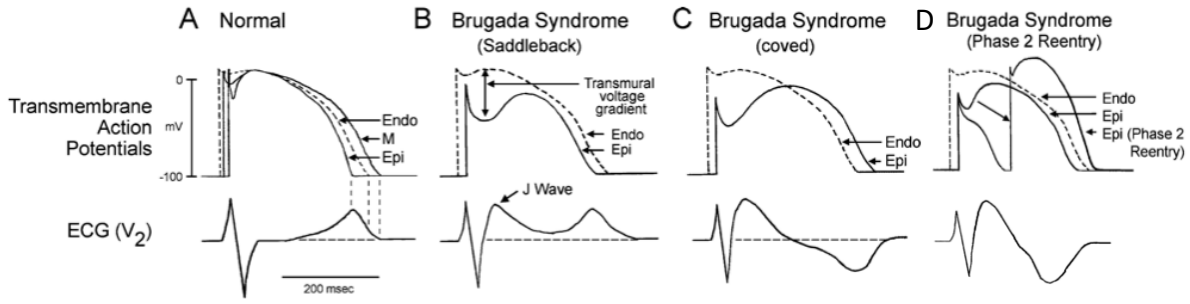

FIGURE 1: *Schematic representation of right ventricular epicardial action potential changes proposed to underline the ECG manifestation of the BrS. Modified from Antzelevitch[18] with permission. Endo, endocardium; M, myocardium; Epi, epicardium; ECG, electrocardiogram.*

3.6 Genetic factors and tests in BrS

Brugada syndrome is an inherited condition transmitted in an autosomal-dominant way with incomplete penetrance[17]. Nevertheless, due to its variable expressivity, it can be sporadic in a significant proportion of patients. Consequently, an individual can be affected of BrS in absence of family history related with this disease.

Since the identification of the first SCN5A gene related to BrS[39], more than 450 pathogenic variants have been identified in 24 genes encoding sodium, potassium, and calcium channels or associated proteins[5,9]. Some of them are: GPDI-L gene (with the mutation A280V, that induces the sodium channel loss of function), KCNJ8 gene (which encodes for a subunit related with the potassium channels) and CACNA1c, CACNB2b and CACNA2D1 genes (encoding calcium channels). However, the role for these genes remains unclear, it seems that all of them could explain a BrS phenotype due to ion current imbalance. Other genes, such as SCN10A, MOG1, MYH7 and HCN4 have also been recently related[19].

Despite all these genetic findings, only 20-30% of BrS patients are genetically diagnosed, of which, approximately 14-25% have positive genetic test for SCN5A mutation[5], which means that the disease is genetically heterogeneous[9,18,19]. Current guidelines only recommend performing a genetic test of the SCN5A gene in family members of a successfully genotyped proband, giving the opportunity to identify asymptomatic familiars at risk of being affected[6,8].

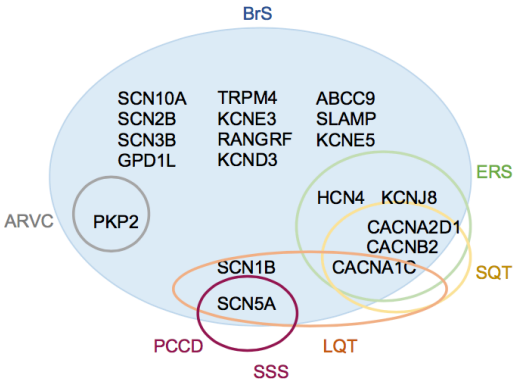

FIGURE 2: *Diagram showing genes associated with Brugada syndrome (BrS) and other overlapping diseases. AF: atrial fibrillation; ARVC: arrhythmogenic right ventricular cardiomyopathy; PCCD: progressive cardiac conduction disease; SSS: sick sinus syndrome; LQT: long QT syndrome; SQT: short QT syndrome; ERS: early repolarization syndrome. Reproduced with permission from Sarquella-Brugada et al.*[8].

3.7 Clinical presentation

The phenotypic expression of BrS varies from completely asymptomatic individuals, who are the vast majority, to SCD at a young age[9,52]. The disease typically manifests in the fourth decade of life, and despite being considered a rare syndrome in children[6,15], the most severe with the highest mortality rate have been observed during childhood[1,3,16,51,37].

Clinical manifestations of symptomatic BrS include unexplained syncope episode and aborted SCD[9] due to ventricular arrhythmias (VT or VF)[33]. The polymorphic VT is more frequently related with BrS, although the monomorphic VT is the most prevalent in children[8,18], which often terminates spontaneously in them. That type of arrhythmias typically occurs at night or at rest, bradycardia-related situations[8,9]. Among other rhythm disturbances, a non-negligible proportion of Brugada patients may suffer from sinus node dysfunction, which ranges from asymptomatic sinus bradycardia or chronotropic incompetence to atrial standstill (asystole), or supraventricular arrhythmias, mainly atrial flutter or fibrillation. Atrioventricular block, complete RBBB or diffusely prolonged QRS complexes have been also associated with BrS, being a reason for suspecting it.

In contrast, some affected patients can also be completely asymptomatic and turn out to symptomatic later[2], giving more importance to an early approach and identification of people at risk.

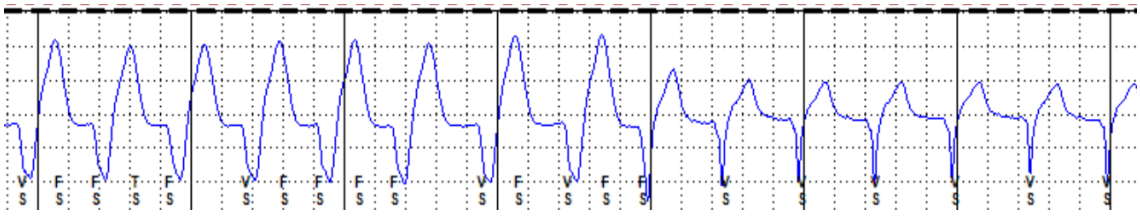

FIGURE 3: *Subcutaneous holter register of monomorphic ventricular tachycardia that terminates spontaneously, in a patient from our series.*

3.8 Diagnostic management

Electrocardiogram is essential for the diagnose of BrS. It has been described as different electrocardiographic patterns of BrS[13,18,19,32], but according to the Report of the Second Brugada Consensus Conference in 2005[13], only the type I Brugada pattern is diagnostic[17-19,32,33,50]:

- The Type 1 consists of a coved-type ST segment elevation followed by a descending negative T wave in at least one right precordial lead (V_1 to V_2

and, less frequently V_3. The specific morphologic characteristics are: at the end of QRS (which is longer than the QRS of a RBBB), an ascending and quick slope with a high take-off ≥ 2mm followed by a concave or rectilinear downsloping ST (in comparison to the isoelectric baseline). There is no clear r' wave and the high take-off often does not correspond with the J point. At 40ms of high take-off, the decrease in amplitude of ST is ≤4mm (in RBBB and athletes could be much higher), and at the end, the ST segment is followed by a negative symmetric T wave.

- The type 2 pattern is a saddleback pattern, characterized by a high take-off of r'≥ 2mm (that often does not coincide with J point). The descending arm of r' coincides with the beginning of ST, and its ST-segment presents an ascent ≥ 0.5mm. Then, the ST is followed by positive or biphasic T wave in V_2 (T peak > ST minimum > 0) and of variable morphology in V_1. Type II is more common in V_1-V_2 and less frequent in V_3 as well.
- The type III pattern shows a right precordial ST-segment elevation ≤1mm either with a coved-type or a saddleback morphology.

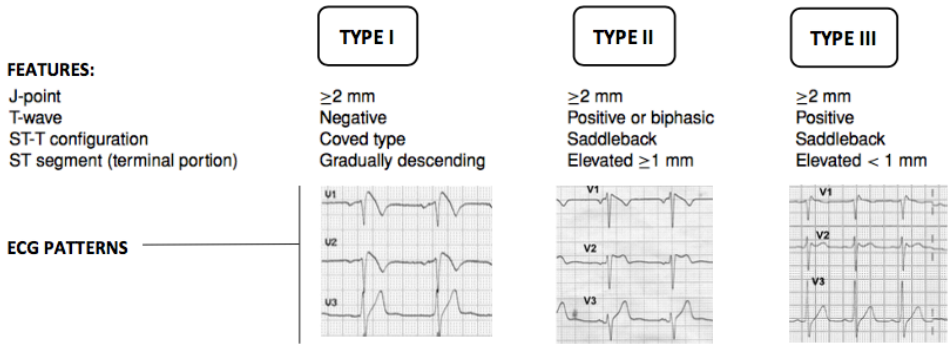

FIGURE 4: *Features of ECG patterns associated with Brugada syndrome. Modified from Mashar[12] and Berne[17] with their permission.*

Brugada syndrome is diagnosed in patients with[11,13,33]:

1. ST-segment elevation with type 1 morphology ≥2mm in ≥1 lead among the right precordial leads V_1-V_2, positioned in the 2nd, 3rd, or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs (AAD).
2. Type 2 or type 3 ST-segment elevation in ≥1 lead among the right precordial leads V_1-V_2, positioned in the 2nd, 3rd, or 4th intercostal space

only when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type I ECG morphology.

It can present some clinical features that help to increment the consistency of the diagnose, but they are not specifically necessary for getting it. These are:

- Previously documented ventricular fibrillation (VF) or polymorphic ventricular tachycardia (VT), inductility of VT with programmed electrical stimulation, unexplained syncope, febrile seizures, an episode of aborted SCD and/or nocturnal agonal respiration.
- Family history of SCD younger than 45 years old and/or coved-type ECG pattern in family members, unexplained syncope or nocturnal agonal respiration.

Despite the three ECG patterns related with BrS can be observed in the same patient at different times, type 2 and type 3 pattern are suggestive, but not diagnostic of it[9,17]. Finally, drug induced conversion from normal ECG to a type 2 or type 3 pattern is considered inconclusive[18].

The performance of an ECG in patient with suspected BrS has some peculiarities. Some studies demonstrated that during the ECG acquisition, the placement of the right precordial leads in more cranial position (up to the second intercostal space above normal) in addition to the standard fourth intercostal space, can increase the sensitivity of the ECG detecting the Brugada phenotype[18,32,33] in some patients, both in the presence or absence of a drug challenge. That special localization correlates with the anterior right ventricular outflow tract (RVOT), the region generally most affected in BrS[11,13]. False-negative test can result from not paying attention to these high-placed leads[16].

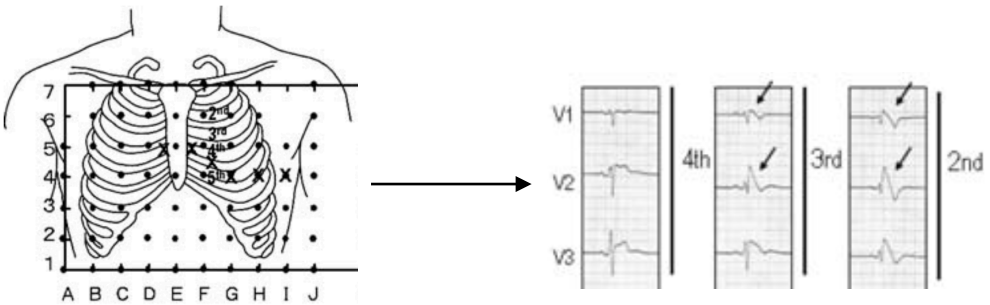

FIGURE 5: *Shift of right precordial leads to 2nd and 3rd intercostal spaces unmasks a type 1 Brugada ECG. Modified from Antzelevitch[13] with their permission.*

A diagnostic-type I Brugada pattern is not always easy to find. It's true that, for instance, Corcia et al.[37] found out an abnormal baseline ECG in 75% of young patients who presented with lethal events during follow-up. In contrast, spontaneous diagnostic Brugada ECG pattern is only observed in a 25% of tracings and most ECG will normalize at a follow-up[2,6], due to its fluctuating character[1,18,19,23,32], fact that confers difficulties in BrS diagnosis. In consequence, further tests are mandatory for uncertain diagnostics and risk assessment.

It has been identified modulators that play a major role in the dynamic nature of the ECG and may also be responsible for ST-segment elevation unmasking the Brugada ECG diagnostic-pattern[32]. Bradycardia and vagal tone may contribute by decreasing calcium currents, fact that explains the greater ST-segment elevation recorded in vagal settings[26] and the higher incidence of ventricular arrhythmias at night[8]. One of the most well-known precipitating factor, especially among pediatric population, is fever[14,21]. The $Na_v1.5$ sodium channel has shown to be a temperature-dependent ionic channel[21] and, at higher temperatures, the premature inactivation of it is accentuated. So, it is crucial trying to record an ECG during a febrile episode[21] or few minutes after an atypical febrile convulsions, relatively common occurrences in childhood. Other important modulators are sodium channel blockers, anesthetics, some drugs and oral medication (antidepressants or antiarrhythmics) and ionic imbalance (hyperkalemia and hypercalcemia)[8,10,13,23].

3.9 Sodium channel blockers challenge

When there is clinical suspicion of BrS in absence of spontaneous type I ST-segment elevation may be unmasked by administration of intravenous class IC antiarrhythmic agents (ajmaline, flecainide, procainamide, pilsicainide) which act as sodium channel blockers[17-19,33,50]. The test should be monitored with a continuous ECG recording and be finished when the coved-type I ECG develops (giving as a positive), premature ventricular beats or other arrhythmias appear, or QRS widens $\geq$130% of baseline[13]. Ajmaline seems to improve the diagnostic efficiency better than flecainide[27]. However, it is not a risk-free diagnostic tool[25,27], especially in pediatric population, in which could cause life-threatening arrhythmias (Conte et al. [25] registered an incidence of 1.8%) . For this reason, the

test should be done in a safe environment with a life-support equipment and two external defibrillators available.

Because nearly 25% of drug-induced tests may result in a false-negative result, particularly in children where exist an age-dependent response to ajmaline, a repeat test after puberty (>15 years old) should be considered[17,27].

3.10 Differential diagnosis and associated diseases

The characteristic ECG Brugada pattern that may arise from multiple causes and disappear upon resolution of the injury has been named *Brugada phenocopy*[17,32]. At least, these clinical entities should be carefully considered and ruled out during the diagnostic process (*Figure 6*).

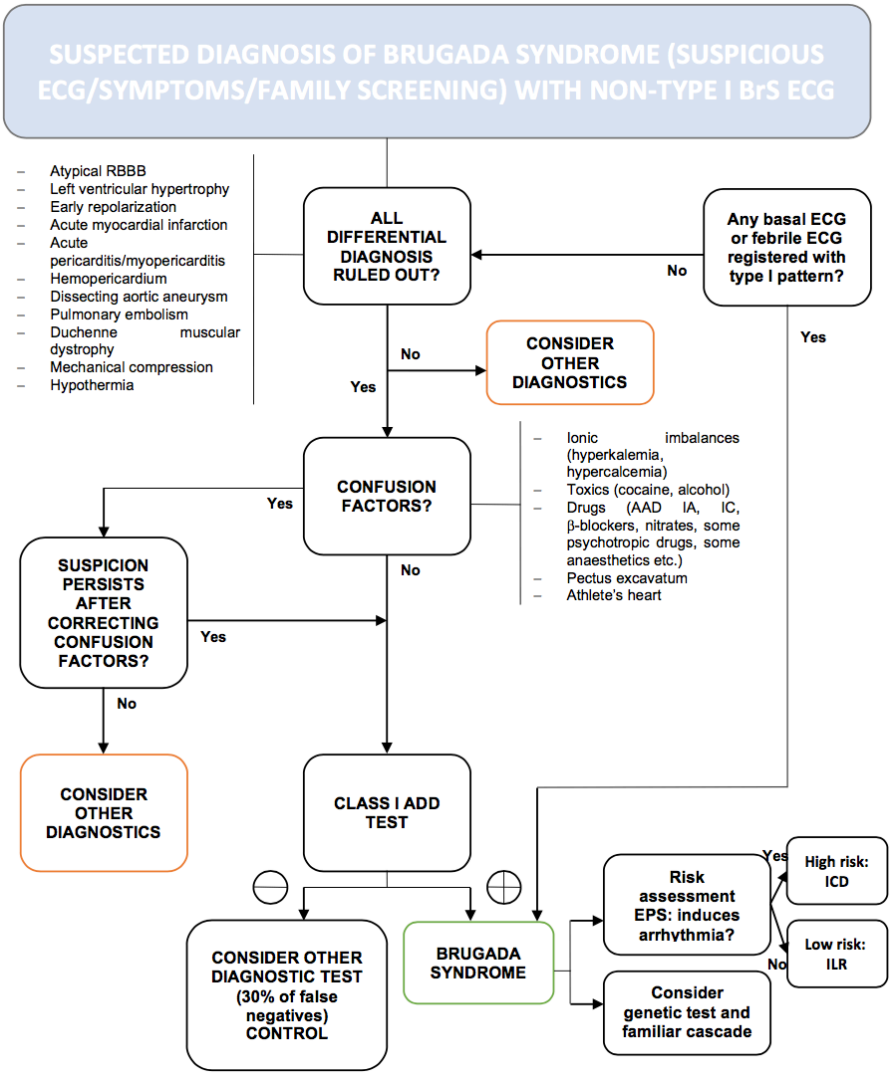

FIGURE 6: *Diagnostic algorithm for BrS. Adapted with permission of Brugada[17] and Cruz[27]*. ECG, Electrocardiogram; ADD, Antiarrhythmic drug; EPS, Elegrophisiology study; ICD, Implantable cardioverter defibrilator; ILR, Implantable loop recorder.

The genetic heterogeneity of inherited conduction disorders often show overlapping syndromes which include long QT syndrome type III, Brugada syndrome, atrial fibrillation, progressive cardiac conduction disease or Lev-Lenègre syndrome, early repolarization syndrome, first degree atrio-ventricular block and sick sinus syndrome. The array of phenotypes exhibited in these syndromes, is mainly due to pathogenic variants in the SCN5A gene[8].

3.11 Risk assessment and prognosis

An accurate arrhythmic risk stratification is mandatory to identify high-risk patients of suffering cardiac arrhythmic events, who could benefit from an implantable cardioverter defibrillator (ICD). However, nowadays, it still remains a clinical challenge[35], especially among pediatric population due to their peculiarities and the lack of published data[31].

A previous episode of aborted SCD and malignant syncope are the strongest predictors of presenting future ventricular arrhythmias[14,17,28,35,37,51], especially if they appear in combination with a spontaneous type I ECG at baseline[14,35]. Other markers of higher arrhythmic risk are the presence of fragmented QRS (f-QRS)[30,35], early repolarization abnormalities in lower or lateral leads, an effective ventricular refractory period (VRP) <200ms, spontaneous atrial flutter or fibrillation, prolonged QTc interval, PR interval or QRS complex, male gender and elder population where exists a marked decrease of the conduction velocity that may contribute to the arrhythmogenic substrate[17]. The value of inducibility of sustained ventricular arrhythmias during an EPS as a tool to evaluate arrhythmic risk in BrS is still controversial[35]. Brugada et al[28] and other studies[36,37] found that inducibility during an EPS is an independent predictor for cardiac events, but other registers have failed to demonstrate it[37,52,56-58]. Finally, neither family history of SCD nor a SCN5A mutation[15,28,35,37,51] have proven to be a risk marker in any of the large studies. However, some specific types of mutations, for example, those that result in a truncated protein might cause a worse BrS phenotype[8].

3.12 Clinical management

The management of a child with suspected BrS should be divided according to his/her symptomatology[16]:

Symptomatic child: a child is not, usually, the first symptomatic member of a family but, the presence of symptoms before diagnosis in combination with ECG abnormalities at baseline is known that constitutes an important risk predictor[2]. In the case of a rhythm abnormality or clinical event, the first diagnostic step consist of performing a 12-lead ECG at baseline of the patient and first-degree relatives. It is important to obtain new tracings in febrile episodes or convulsions as well as treat it immediately[21]. Pharmacological test to unmask the Brugada ECG pattern is the standard diagnostic method. Once diagnosed, genetic test should be performed if it exists a family history related with BrS. Genotype-positive individuals should be closely followed-up to identify possible clinical manifestations[8,14,16,17].

Asymptomatic child: asymptomatic pediatric relative with family members at study or diagnosed of BrS correspond to the majority of cases seen in pediatric arrhythmias units. The follow-up includes a 12-lead ECG every 6 month until adolescence and yearly during childhood[24]. As in the previous case, at least one ECG should be recorded during a febrile episode or convulsions during childhood[21]. In selected cases with family history of SCD, a provocative test could be considered, starting at the age of five years[16,17]. Genetic testing is recommended in the index case and in first-degree family members after having successfully genotyped the proband. All patients should be followed-up, including those with negative tests. EPS should be performed in every diagnosed patient to stratify his/her risk[38,49]. If ventricular arrhythmias are induced, an ICD is recommended (Class IIb). On the contrary case, in our center is considered the implantation of a loop recorder.

Finally, all patients with BrS, regardless of their estimated risk, should be advised to avoid all drugs that may induce a type I ECG and/or trigger VT/VF. The complete list can be consulted at: www.brugadadrugs.org[60].

3.13 Implantable loop recorder

The implantable loop recorder (ILR) is a small subcutaneous device (44.8mm x 7.2mm x 4.0mm) which is implanted in a minimally invasive way, just under the skin of the chest for cardiac monitoring (*Figure 8*). The ILR monitors the electrical activity of the heart, continuously storing information in its circular memory (the "*loop*" of the name) as electrocardiograms. Abnormal activity such as arrhythmia

is recorded by “freezing” a segment of the memory for later review[61]. Recording can be activated in two ways. First, automatically due to the detection of arrhythmic events or according to heart rate ranges previously defined and set in the ILR by the physician. If the heart rate drops below, or rises above the set rates, the ILR will record without the patient’s knowledge. The second way is through a patient-activation whereby the patient triggers a symptom driven recording (SDR) by pushing a button as a result of symptoms like skipped beats, lightheadedness or dizziness. In consequence, the ILR records by capturing the electrical information preceding, during and after the symptoms in the format of an ECG. The physician can download and review the recorded events during an office visit using a special programmer or by remote monitoring[62]. Because of the ILR's long battery life (3 to 4 years), the heart can be monitored for an extended period. From the first version, ILR has been improved, being able to record other multiple signals in addition to the ECG (e.g. blood flow or pressure, EEG etc.)[40].

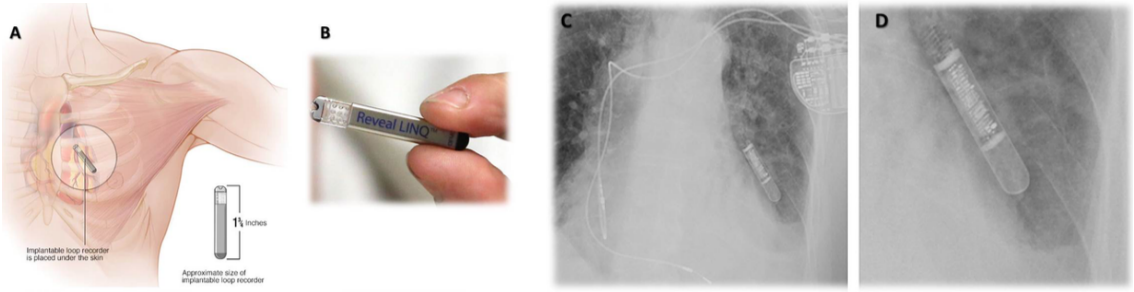

FIGURE 7: *The implantable loop recorder is a small subcutaneous device implanted under the skin of the chest for up to three years (A, B). Chest radiographs (PA projections) of an implanted loop recorder (C,D): note the dimension comparison with a modern implanted dual-chamber pacemaker.*

When a ILR could be considered?

ECG loop recorders should be considered in diagnosed Brugada patients in the absence of high-risk criteria for life-threatening arrhythmias that requires immediate treatment[44]. These are asymptomatic patients or patients with a history of unexplained syncope with spontaneous or drug-induced type I ECG Brugada pattern[41]. Remind that its uses are based on expert opinion, so, no level of scientific evidence has been specified[43]. The purpose of this strategy is keeping monitored patients with Brugada syndrome stratified as low-moderate risk and detect any electrocardiographic changes being a tool guide for the treatment[40].

Technical aspects[40]

The auto-activation of the ILR can be compromised by the detection of false arrhythmias and the missed detection of true arrhythmias. Documented causes of false arrhythmias storage include: undersensing related to sudden reductions in R-wave signal amplitude during both normal sinus rhythm and arrhythmias and undersensing by transient loss of ECG signal related to device amplifier saturation, T-wave and myopotential. The prevalence of misdiagnosis is unknown and it is clearly a priority of research to solve.

Like all implanted devices, ILRs also carry the risk of pocket infections, which account for 1-3% of patients. It could be during either the periprocedural phase or late during the follow-up, that resolve with device explantation.

MRI scanning of ILR patients can be performed without any harm to patient or device, but artefacts that could be mistaken for a tachyarrhythmia are seen frequently[45]. So, further clinical studies are needed to investigate whether modified MRI techniques are helpful to eliminate these imaging artifacts[46].

3.14 Therapeutic options

To date, the implantable cardioverter defibrillator (ICD) is the only proven effective therapeutic strategy for the prevention of SCD in BrS patients[12,47-49]. Its implantation is a Class IA indication in patients with BrS and a history of either ventricular arrhythmias or aborted SCD (*Annex VII*). Despite its effectiveness, ICD placement is frequently associated with device-related complications, of which, the most prevalent are led failure and inappropriate shocks[12,47-49]. In order to avoid these problems, new subcutaneous ICDs has been proposed to use.

An alternative is pharmacological treatment with the objective of rebalancing the ionic current. Isoproterenol, a L-type calcium channel current increaser, is only useful when an arrhythmic event appears, during the acute phase. In contrast, quinidine acts by stabilizing the transient outward ionic currents (I_{to}) and converting them from polymorphic to monomorphic, improving clinical tolerance of the arrhythmia. This drug can be useful as a chronic treatment, as a bridge therapy to ICD, as an alternative to it or as a combination with the ICD, depending on the patient's individual risk[17]. Recently, epicardial radiofrequency catheter ablation over RVOT has emerged as a potential treatment in patients with recurring episodes, but this therapeutic option is not well-defined yet[8,50].

4. JUSTIFICATION OF THE PROJECT

To date, the implantable cardioverter defibrillator (ICD) remains the only tool that has proven to be effective in reducing the mortality of patients with Brugada syndrome, treating potentially lethal arrhythmias in more than 25% of cases, as demonstrated by the recent publication of Gonzalez et al.[16]. Showing this high effectiveness, it would be easy to think that it would be a very good strategy for pediatric patients with BrS. However, these same studies stand out the high incidence of complications and inappropriate shocks that children with ICD receive[52]. Moreover, ICD are difficult to be adapted in children, as the body grows, there is the need of electives revisions/re-implantations, and the long patients' life expectancy request a greater number of the generator substitutions. In the pediatric population, when and to whom to implant an ICD not only generates controversy, but it is an absolute unknown, since in order to stratify their risk, it tends to extrapolate the protocol of adults to children assuming that the pathology behaves the same in both populations. For this reason, it is essential to improve stratification in children, helping to classify when and which need ICDs and which do not.

The implantable loop recorder (ILR) is a small device that combines the prolonged electrocardiographic record and a remote monitoring system with a low degree of invasiveness. It allows a comprehensive follow-up of the ECG, without the need for multiple hospital visits. There are several studies that evaluate ILRs in patients with arrhythmic events in general population[42,43] and one in BrS patients[41]. Unfortunately, there is few data in pediatric patients with suspected arrhythmia[44] and no studies, to date, that have been dealt with pediatric patients with BrS. This gap leaves them without an early detection of arrhythmias (important for risk stratification) or a diagnosis facing a syncopal event (to really know the syncope's etiology: vasovagal, cardiac, neurological etc.). In our study, we are going to intend to respond to this gap in the pediatric population since we believe ILRs can provide useful supplementary information as well as specify etiology of an unexplained syncope, helping in improving the stratification of pediatric patients with BrS who, at first, do not have strict indications of ICD and getting a more adjusted treatment that, in short and long term, will significantly improve the quality of life of the patients with BrS.

5. HYPOTHESIS AND OBJECTIVES

5.1 Hypothesis

The remote monitoring by implantable subcutaneous holter will allow the detection of arrhythmic events in pediatric patients with non-high-risk Brugada syndrome, helping in their risk stratification and guiding to therapy.

5.2 Objectives

Primary objectives

- To quantify the incidence of arrhythmic events recorded by ILR in pediatric patients with non-high-risk Brugada syndrome.
- To analyze the frequency of correlation between clinical symptoms and rhythm abnormalities detected by ILR.

Secondary objectives

- To describe demographical data and clinical characteristics of anonymized pediatric patients with BrS of Hospital Sant Joan de Déu.
- To early detect significant conduction abnormalities in pediatric patients with BrS requiring further treatment.
- To determine the factors that influence the appearance of arrhythmias in pediatric patients with BrS in order to improve and refine the clinical management.

6. METHODS AND MATERIALS

6.1 Study design

It has been designed a retrospective cohort study in order to analyse the data recorded by subcutaneous holter implanted in pediatric patients with non-high-risk Brugada syndrome, followed at San Joan de Déu Hospital, in Barcelona.

6.2 Study population

The study population was based on pediatric patients with non-high-risk Brugada syndrome (BrS) followed at the Pediatric Arrhythmia Unit of Sant Joan de Déu Hospital, in Barcelona.

6.2.1 Inclusion criteria

- Pediatric patients under the age of 21 years old at the time of inclusion.
- Individuals with diagnostic ECG pattern of Brugada syndrome occurring spontaneously, after provocative drug test or appeared during a febrile episode (*section 3.8*).
    - Symptomatic or asymptomatic.
    - Positive genetic study (with or without identified casual mutation) or not done.
- Patients who perform an electrophysiology study (EPS) and no sustained ventricular arrhythmias or ventricular fibrillation were induced.

6.2.2 Exclusion criteria

- Patients with BrS and personal history of either ventricular arrhythmias (VT or VF) or aborted SCD who have strong clinical indication for ICD.
- Type 2 or 3 Brugada pattern in basal ECG that does not change to type 1 pattern with pharmacological test or fever.
- Individuals who performed EPS and sustained ventricular tachycardia or ventricular fibrillation were induced.
- Patients carriers of ICDs or pacemarkers previously to the study.

6.3. Sample

A non-probabilistic consecutive sampling method was performed from our study population. Finally, a total of 34 anonymous patients followed at the Pediatric Arrhythmia Unit of Sant Joan de Déu Hospital from 2015 who accomplished all the inclusion and none of the exclusion criteria, were included in the study in a completely anonymous way.

In order to calculate our sample's statistic power, it was used the Prof. Marc Saez' software based on the library 'pwr' of the free statistical environment R (version 3.5.1). In a bilateral contrast, with an alfa level of 5% and a sample of 34 patients, to detect an average difference (up to 30%), we had a statistical power of 54%.

6.4 Study variables

Different variables were registered initially and during follow-up patients in their medical records as part of the normal healthcare process. Before performing any tests, nurses explained to each patient the medical procedure that was going to be done, after the informed consent was obtained.

An exhaustive physical examination, a careful personal and family medical history, a baseline 12-lead ECG or a provocative test with ajmaline in cases of normal baseline ECG and an electrophysiological study was initially performed to each patient. Once the non-induction of sustained ventricular arrhythmias during EPS was assured, the option of placing an ILR was recommended. The possible presence of underlying structural cardiac abnormalities was evaluated in all patients by transthoracic echocardiography, despite not being an exclusion criteria.

Dependent variable

Arrhythmic event

An arrhythmic event is defined as an irregularity or loss of rhythm manifested in the ECG. Some rhythm disturbances have more incidence in patients with BrS (*section 3.7*). Those that more frequently lead to death and, therefore, the most important ones to detect are ventricular arrhythmias. These are:

- Monomorphic ventricular tachycardia defined as an arrhythmia with constant electrocardiographic configuration and a stable rate within a few beats.
- Polymorphic ventricular tachycardia, arrhythmia that has a changing rate and demonstrated varying configurations.
- Ventricular fibrillation defined as rapid and continuously varying electrocardiograms with irregular cycle lengths.

When these last more than 30s, are called as sustained arrhythmia. Apart from ventricular arrhythmias, other rhythm disturbances to consider were:

- Sinus node dysfunction manifested as inappropriate sinus bradycardia according to age and activity level, sinus pause/arrest >2.5s, or chronotropic incompetence (failure to achieve 85% of the age-predicted maximum heart rate during the exercise test).
- AV blocks manifested as an extension of PR interval over 200ms.
- Supraventricular (SVEs) and/or ventricular extrasystoles (VEs) defined as an extra beat originated in the atriums or ventricles respectively.
- Atrial arrhythmias defined as sustained atrial tachycardia, atrial fibrillation, and atrial flutter.
- Spontaneous changes in the repolarization pattern compatible with dynamic BrS.

The presence of arrhythmic events was recorded by implantable subcutaneous holter (*section 3.13*). The procedure of its implantation was carried out in the electrophysiology room in all pediatric patients with non-high-risk BrS. It consisted of:

- The administration of subcutaneous anesthesia: 5% Lidocaine 4.5ml + 0.5% Bupivacaine 4.5ml + 1M/ml bicarbonate in the left submammary midthoracic region. Massage the area.
- Insertion, for all patients, the same subcutaneous holter (Revel® LinQ, Medtronic), using the kit insertion of the package and fitted with continuous monitoring and symptom-driven activation functions.

- Performance of patient-specific programming of tachycardia and bradycardia zones, taking into account patient age, medications, and previous documented arrhythmia data (when available).
- Close by approximation with surgical glue (Dermabond) and placement of porous dressing.

Once the device placement finished, it had to set up by application or interrogator and activation of the remote monitoring system. Finally, a registration in the remote monitoring website and the formation of the family for the use of the domiciliary system was required (*Annex III*).

Co-variables

Demographic data

Age (years), sex (male or female), age at LINQ implant (years), months of follow-up (months) and time to first ILR symptom (months).

Family history

Family tree up to three generations with a history of aborted or not sudden death at younger than 45 years old, febrile seizures, epilepsy, rhythm disturbances, carriers of pacemakers, repeat unexplained abortions, diagnosis of BrS (circumstances and therapeutic management) and genetic studies performed.

Clinical data

- *Personal medical history*: it was asked specifically for cardiac and/or neurological antecedents. The reason for considering these antecedent remains in *section 3.10*, where possibly associated diseases have been mentioned.
- *Reason for suspecting BrS*: it was classified in three groups:
    - Familiar screening (family history related with BrS, with or without genetic tests performed) or a personal genetic mutation related with BrS founded in other circumstances (*section 3.6*).
    - ECG rhythm disturbances at baseline or during a febrile episode.
    - Clinical suspicion: when symptoms related with BrS are present (unexplained syncope, pre-syncope, febrile seizures, dizziness, chest pain during fever, nocturnal agonal awakenings etc.).

Unexplained syncope is defined as a non-traumatic and reversible loss of consciousness caused by either ventricular arrhythmias or vasovagal events (those occurring during abrupt postural changes, exposure to heat and dehydration, emotional reactions to events such as blood drawing etc.). Pre-syncope is defined as feeling of imminent faintness, although without reaching a complete loss of it, happening only a postural hypotonia.

- *Asymptomatic* or *symptomatic*: patients were considered symptomatic if they presented any clinical manifestations related to BrS included unexplained syncope and/or aborted SCD. Arrhythmic syncope was suspected in the absence of prodrome or specific triggering circumstances. Patients with clinical diagnosis of vasovagal syncope were not considered as symptomatic.
- *Usual medication*: the active ingredient of the drug, dose and posology.

12-leads baseline ECG

12-leads baseline ECG was recorded to all patients using a *CardioTech^{TM} GT-400 ECG Machine*. It was considered diagnostic of BrS if a coved-type ST-segment elevation of ≥2mm was documented in ≥1 lead from V_1 to V_3 spontaneously or after a sodium channel blocker (*section 3.8*).

Provocative test

Provocative test with ajmaline was performed in cases of normal baseline electrocardiogram. The test was carried out in the electrophysiology room with a life-support equipment and two external defibrillators available in the room (*Zoll M Series Defibrillators*). A peripheral intravenous access was placed and an ajmaline intravenous infusion (maximum dose of 1mg/kg) was administered over a 5-min period. In patients younger than 5 years old, the test was performed under drug sedation by a single intravenous bolus of propofol. Ajmaline is deactivated quickly and its effects wear off after a few minutes. Therefore, it was monitored until the ECG normalized. During the test, it was continuously monitored the patient's cardiac rhythm, hemoglobin saturation and arterial pressure. Ajmaline infusion was terminated before reaching the target dose if type 1 ECG pattern in ≥ 1 right precordial lead (V_1-V_3), QRS prolongations >30%

of baseline, frequent premature ventricular beats, high-degree atrioventricular blocks or sustained ventricular arrhythmias (VT or VF) was documented. Once the test was finished, a cardiac monitoring during 30 minutes was left.

All baseline and drug-induced 12-lead ECGs were recorded at a paper speed of 25mm/s and amplitude of 10mm/mV, with the right precordial leads positioned at the sternal margin of the third and fourth intercostal space according to the guidelines[33] (*Figure 5*). Two independent experienced pediatric cardiologists of the Unit of Pediatric Arrhythmias analyzed all the ECG. In case of disagreement, a third physician was consulted. PR interval, QRS duration, and QTc interval (determined using Bazett's formula) were measured in milliseconds (ms) by averaging hand measurement on three consecutive beats. Maximal ST-segment elevations were measured at the J point in the right precordial leads (V_1-V_3), and analyses of ST-segment elevation were performed in leads V_1 and V_2. The presence of R waves in aVR and QRS fragmentations were identified and noted[30]. Moreover, ECGs were reviewed to identify sinus node dysfunction (SND) and atrial arrhythmias.

Genetic test

Genetic testing with sequence analysis of SCN5A gene was recommended for pediatric patients with first degree relatives diagnosed of BrS with a positive genetic test and pediatric patient diagnosed with BrS. In this last case, if a mutation-positive was obtained, a family cascade screening in first degree relatives was proposed.

Sequence analyses of SCN5A were performed by extracting genomic DNA from peripheral blood leucocytes or saliva samples: if the patient had a peripheral intravenous access (for other procedure), a blood sample in an EDTA tube was taken. If not, in order to avoid an invasive procedure of blood extraction, a saliva sample was taken using a DNA Genotek Oragene 06-500 kit. Genomic DNA was extracted from these samples, using Chemagic® (Chemagen Systems, Germany). All genes studied are related with BrS (*section 3.6*): it was collected the gene or genes analyzed, in addition to data on the variants identified in each gene analyzed (location, population frequency, *in silico* prediction, type of variant and information from international databases on the variant found).

Electrophysiological study

Electrophysiological study was performed in all pediatric patients with the purpose of risk stratification. In individuals younger than 12 years old, study was performed under propofol sedation. Intravenous accesses were gained using right femoral venipuncture, and single catheters were used to determine baseline intervals and to stimulate the heart.

Baseline intervals were measured including the AH (shows the conduction time through the AV Node) and HV interval (displays the conduction time from the His bundle to the first identifiable onset of ventricular activation). Evaluation of sinus node disfunction (SND) was performed which included measurement of sinus node recovery time (SNRT), corrected SNRT, and sinoatrial conduction time estimated using the method described by Narula et al. The atrioventricular conduction system was evaluated by measuring the Wenkeback cycle length and the atrioventricular nodal effective refractory period in each case. Patients with either history of palpitations or evidence by ECG monitor of supraventricular tachycardia, an atrial stimulation protocol was also performed. The ventricular stimulation protocol consisted of a maximum of three ventricular extrastimuli with a minimal coupling interval of 200ms delivered from ≥1 ventricular site. Results were considered positive when sustained VT or VF were induced. In that case, the patient was excluded from our study.

This test was performed with *Philips Allura Xper FD20/10 biplane* mixed with cardiovascular X-ray guidance system, and X-ray protection was mandatory in all personal present in the EPS room during the procedure.

6.5 Follow-up

Clinical follow-up of patients consisted of physical examinations and ECG after ILR implantation. Follow-up of the device was performed at 1 and 3 months after implantation and thereafter every 6 months. The ILRs memory looking for arrhythmic events was reviewed at least once a week by two expert pediatric cardiologist independently, and each time that the activation of ILR was provoked by symptoms or by the patient. Device memory was also interrogated in each regular visit.

6.6 Data acquisition

All the data used in the study, included the ECGs recorded by ILR, were extracted from the medical history of pediatric Brugada patients followed at Arrhythmia Unit of Sant Joan de Déu Hospital, in a completely anonymous way and numerically codified. The process was made by the Department of Medical Informatics of the centre, registering all data needed in an anonymous database platform hosted on the servers of the hospital. Our Arrhythmia Unit has an internal regulation that allow the double-anonymous review of the database collected of our patients. It was used a general and previously approved CEIC's authorization in order to be able to carry it out. Finally, the database was analysed and exposed to this study.

FIGURE 8: *Study's chronogram from its design to its conclusions. CEIC: Comitè Ètic d'Investigació Clínica de SJD Hospital. Their authorization has been included in Annex II.*

6.7 Statistical analysis

The statistical analysis was carried out using the IBM SPSS® software package (version 10.0, SPSS Inc., Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

For the univariate analysis, the presence of arrhythmic events (dependent categorical dichotomous variable) were presented as a proportion with its confidence interval (IC 95%). The quantitative continuous variables were described as mean ± standard deviation (those with normal distribution) and with median and interquartile range of 25-75 (those without normal distribution). To compare the co-variables with the presence of arrhythmic events, a bivariate analysis was applied: a Chi-square of Pearson test (x^2), was used to co-relate qualitative variables whereas to analyze quantitative variables (age) with the mentioned dependent variable, an unpaired t-student test (normal distribution) or Mann-Whitney U test (without normal distribution) were used. A multivariate analysis was carried out using the free statistical environtment® software package (version 3.5.1). A regression logistic model (method: enter) was used, in order to know which co-variables were associated with the presence of an arrhythmic event.

7. ETHICAL CONSIDERATIONS

This project complies with the ethical principles of the *Declaration of Helsinki* about researching involving human subjects established by the World Medical Association. Before beginning our study, the correspond protocol was evaluated by the Clinical Research Ethical Committee of Fundació Sant Joan de Déu Hospital, in Barcelona.

According to the legal framework of human rights and data confidentiality specified in Organic *Law 15/1999* on the Protection of Personal Data (LOPD), data was registered and analyzed anonymously and under non-identifying numeric codes. The author did not have access to any confidential information of the patients which was only used for the purpose of the research.

It was followed the *Law 41/2002* of 14 November, that regulates the autonomy of the patient and their right to information and clinical documentation and *Royal Decree 1720/2007 of December 21* that regulates the security of files containing patient data. After receiving the appropriate information, the patients voluntary signed an informed consent for implantable subcutaneous holter for being an invasive procedure (*Annex I*), information contained in the *Law 14/2007* for invasive procedures. Legally, in the case of minors (in medical terms, below 16 years old), their parents or legal tutors were responsible for signing the informed consent. However, the under-age patient was also properly informed and his/her agreement was considered. From age 7 to 16, patient's agreement was fundamental, since it was considered that they could have reasoned decisions.

If a genetic test had to be performed, during all process the Law for investigation on biologic samples was applied (*Law 14/2007* and the *Royal Decree 1716/2011*). In case that a pediatric patient obtained a positive genetic test, a screening process on first-degree relatives should be advised. It that situation, when the doctors need to communicate the finding of a genetic rare disease in the family, the language used must had to be extremely careful and always following the legal and ethical premises.

This study has not any commercial bias nor interests.

8. RESULTS

8.1 Population characteristics

A total of 34 paediatric patients diagnosed with Brugada syndrome younger than 21 years old (mean age 10,5 ± 4,22) were implanted an implantable loop recorder (ILR) and included in our study. Twenty-four were male (70,59%) and ten were female (29,41%). The mean age of male patients was 11,42 ± 3.98 while it of girls was 8,3±3,98. The ILR detected arrhythmic events in eleven patients (32,35%), seven males (29%, *p*=0,538) and four females (40%, *p*=0,538). Thirteen patients (38,24%) had a family history of SCD (6 had arrhythmic events, with a *p*=0,176*)* and four patients (11,76%) presented personal antecedents of cardiac and/or neurological diseases (3 had arrhythmic events, with a *p*=0,052). Previously to diagnosis, nineteen patients (55,88%) were asymptomatic and fifteen (44,12%) were symptomatic. The most prevalent clinical manifestation was syncope (n=8, 53,33%), followed by atypical chest pain (n=3, 20%) and febrile seizures (n=2, 13,33%). In those two last patients were detected arrhythmias during their follow-up (*p*=0,035) (*Table 1, Table 3*).

TABLE 1. Summary of demographics and clinical parameters of patients included

Demographic data	N=patients (%)
Sex	
Male	24 (70,59%)
Female	10 (29,41%)
Mean age	10,5 ± 4,22
Mean male patient's age	11,42 ± 3,98
Mean female patient's age	8,3 ± 3,98
History of family SCD	13 (38,24%)
Personal history of associated diseases	4 (11,76%)
Asymptomatic	19 (55,88%)
Symptoms (previously to diagnosis)	15 (44,12%)
Syncope	8 (53,33%)
Pre-syncope	1 (6,67%)
Febrile seizures	2 (13,33%)
Atypical chest pain	3 (20%)
Nocturnal awakenings	1 (6,67%)
Reason for evaluation	
Family screening	25 (73,53%)
Abnormal basal ECG	4 (11,76%)
Symptoms	5 (14,71%)
Age at LINQ implant	8,35 ± 4,73

Values are n(%) and mean ± DS.
Abbreviations: ECG: electrocardiogram; SCD: sudden cardiac death

8.2 Results regarding the main reason for evaluating BrS *(Table 1)*

- **Family history of BrS** was the main reason in order to evaluate the BrS in 25 patients (73,53%). Of these, 13 patients (52%) had a positive family history of SCD.

- **Abnormal basal ECG**: four patients (11,76%) were evaluated due to the discovery of electrocardiographic alterations related to BrS.
- **Symptoms**: five patients (14,71%) were studied due to symptoms.

8.3 Diagnostic tests performed and their results *(Table 2-3)*

- A basal ECG was performed to all 34 patients. In eight cases (23,53%) it was completely normal, in sinus rhythm without any abnormal ECG wave or intervals. The remaining twenty-six patients (76,47%) showed an abnormal ECG at baseline. Among all rhythm disturbances founded only the fragmented QRS complex showed to be statistically significant with the presence of arrhythmic events (p=0,048) while the QRS complex alteration just showed a certain tendency (p=0,056).
- An echocardiography was performed to all 34 patients and in none structural anomalies were found.
- Twenty-five patients (73,53%) had obtained an ECG during a febrile episode: in nine cases (36%) it was normal while in sixteen patients (64%), the ECG showed a diagnostic type 1 BrS pattern. An ECG could not be obtained during any febrile episodes in nine cases (26,47%). Arrhythmic events were detected by ILR in six patients (38%) with altered febrile ECG pattern (p=0,734).
- Patients with normal ECG at baseline or those who had rhythm alterations in it but non-type 1 ECG pattern, were performed the provocative test with ajmaline. Twenty-nine patients (85,29%) had a positive test inducting a type 1 ECG BrS pattern of which arrhythmic events were detected in 8 cases (28%) (p=0,152). Two patients (5,89%), even though they obtained a negative test, it was agreed and decided to implant them a ILR as well because, the first case presented a clearly altered ECG at baseline and there was suspicious of Lev-Lenègre syndrome while the other case had a family history of SCD, debuted with febrile seizures and obtained an altered ECG with fever. The provocative test was not performed in the three remaining patients, because they had a spontaneous type 1 Brugada pattern at baseline.

- A genetic test was performed to twenty-eight patients. Eight of them (28,57%) were negative from mutations related to BrS. The remaining twenty patients (61,76%) obtained a positive result: thirteen (65%) for SCN5A mutation and seven (35%) expressed other mutations including HCN4, ABCC9, PKP2, SCN1A, CACNA2D, MYH6/MYH7 and CSRP3. Six patients (17,65%) had pending the results of genetic analysis. In none of the genotype-positive cases was obtained statistically significant results (p>0,05).
- All patients underwent an electrophysiological study (EPS): thirteen (38,24%) obtained a completely normal test while the remaining twenty-one patients (61,76%) showed altered parameters, none of them statistically significant (p>0,05). No sustained ventricular arrhythmias were induced during programmed ventricular stimulation in any case. However, in three patients (14,29%) short runs of non-sustained ventricular arrhythmias were induced and rhythm disturbances was detected by ILR during their follow-up (p=0,009).

TABLE 2. Description of test performed and their results

Test performed	**Results (n=patients, %)**		
	Normal/negative/not done	**Abnormal/positive**	
Basal ECG	8 (23,53%)	Positive result Spontaneous type 1 pattern Non-type 1 pattern Complete/incomplete RBBB QRS complex alteration f-QRS PR interval alteration QT interval alteration	26 (76,47%) 5 (19,23%) 6 (23,08%) 15 (57,69%) 11 (42,31%) 6 (23,08%) 4 (15,38%) 1 (3,85%)
Ecocardiography	34 (100%)	0 (0%)	
Febrile ECG abnormal	9 (26,47%)	ECG tracing obtained Normal (negative) pattern Abnormal (positive) pattern	25 (73,53%) 9 (36%) 16 (64%)
Ajmaline test	5 (14,71%)	29 (85,29%)	
Genetic test	6 (17,65%)	Negative result Positive result SCN5A positive Other mutations	8 (28,57%) 20 (71,43%) 13 (65%) 7(35%)
EPS	13 (38,24%)	Positive result VRP < 200ms AH > 120ms HV > 55ms NSTV	21 (61,76%) 11 (52,38%) 4 (19,05%) 5 (23,81%) 3 (14,29%)

Abbreviations: ECG: electrocardiogram; EPS: electrophysiology study; RBBB: right bundle branch block; f-QRS: fragmented QRS complex; VRP: ventricular refractory period; AH: atrio-His interval time; HV: His-ventricular interval time; NSVT: non-sustained ventricular tachycardia. In genetic test, other positive mutations include HCN4, ABCC9, PKP2, SCN1A, CACNA2D, MYH6, MYH7 and CSRP3 genes.

TABLE 3. Comparison of the presence of arrhythmic events between demographic, clinical and diagnostic parameters

	PARAMETERS		ARRYTHMIC EVENTS ⊕ N=11 (%)	ARRHYTHMIC EVENTS ⊗ N=23 (%)	p-value (<0,05) *chi-square(x^2)*
DEMOGRA-PHICS	Age[a]		11 (9,82±5,4)	23 (10,83±3,7)	0,53
	Sex	Male sex	7 (29)	17 (70)	0,538
		Female sex	4 (40)	6 (60)	
CLINICAL PARAMETERS	Family screening		8 (32)	17 (68)	0,942
	Abnormal basal ECG		2 (50)	2 (50)	0,422
	Symptoms		1 (20)	4 (80)	0,523
	Family SCD		6 (46)	7 (54)	0,176
	Associated diseases*		3 (75)	1 (25)	**0,052***
	Asymptomatic		6 (32)	13 (68)	0,914
	Symptomatic	Pre-syncope	1 (100)	0 (0)	0,142
		Syncope	1 (13)	7 (88)	0,170
		Febrile seizures**	2 (100)	0 (0)	**0,035****
		Atypical chest pain	1 (33)	2 (67)	0,970
		Nocturnal awakenings	0 (0)	1 (100)	0,483
		Total	5 (33)	10 (67)	0.914
DIAGNOSTIC TESTS	Basal ECG abnormal	Spontaneous type 1 ECG pattern	2 (40)	3 (60)	0,692
		Non-type 1 ECG pattern	2 (33)	4 (67)	0,955
		Complete/incomplete RBBB	6 (40)	9 (60)	0,458
		PR interval prolongation	2 (50)	2 (50)	0,422
		QRS complex alteration*	6 (55)	5 (46)	**0,056***
		QT interval alteration	0 (0)	1 (100)	0,483
		f-QRS complex**	4 (67)	2 (33)	**0,048****
	Febrile ECG abnormal		6 (38)	10 (63)	0,734
	Provocative test		8 (28)	21 (72)	0,152
	EPS abnormal	VRP<200ms	3 (27)	8 (73)	0,661
		AH>120ms	1 (25)	3 (75)	0,738
		HV>55ms	2 (40)	3 (60)	0,692
		NSVT**	3 (100)	0 (0)	**0,009****
	Genetic test positive	SCN5A	4 (31)	9 (69)	0,988
		Other mutations	2 (29)	5 (71)	0,810

Abbreviations: P-value: probability value (according to chi-square analysis); ECG: electrocardiogram; SCD: sudden cardiac death; RBBB: right bundle branch block; f-QRS complex: fragmented QRS complex; EPS: electrophysiology study; VRP: ventricular refractory period; AH: atrio-His interval time; HV: His-ventricular interval time; NSVT: non-sustained ventricular tachycardia. In genetic test, other positive mutations include HCN4, ABCC9, PKP2, SCN1A, CACNA2D, MYH6, MYH7 and CSRP3 genes.

[a] *Mean (standard deviation).*

**p<<0,1; ** p<0,05*

8.4 ILR findings during follow-up

The mean age at ILR implantation was 8,35 years ± 4,73 and the average follow-up time after it was 17,76 months ± 13,41 (range: 3 to 45 months). A total of twenty-three patients (67,65%) were not detected arrhythmic events during any time of the follow-up. So, the remaining eleven patients (32.29%) were recorded rhythm disturbances, most of the time, being more than one in the same patient (*Table 4*).

Symptoms driven recordings (SDRs)

The mean time from ILR implantation to first symptom was 15,57 months ± 16,65. A total of seven patients (63,64%) activated the LINQ's recording function due to symptom episodes including pre-syncope (the most repeated one among these patients), palpitations, syncope, febrile seizures and atypical chest pain. Of 14 events transmitted by ILR in symptomatic cases, in two patients (28,57%) the ECG tracing showed episodes of non-sustained monomorphic ventricular tachycardia manifested as syncope. The remaining five patients (71,43%) showed normal sinus rhythm, sinus tachycardia and minimal rhythm disturbances such as isolated supra-ventricular extrasystoles.

Actionable ECG tracing in asymptomatic patients

In four asymptomatic patients (36,36%) the ILR recording was auto-activated. In one of those cases (25%), ECG tracing showed various episodes of asymptomatic NSVT lasting less than 20 seconds (*Annex VI*). In the same patient, ILR also reported recurrent phases of asymptomatic sinus bradycardia (down to 40 bpm) with frequent ventricular extrasytoles (*Annex VI*), and episodes of abrupt repolarization changes compatible with a dynamic Brugada pattern (*Annex VI*), fact that also triggered the ILR activation in the three (75%) remaining patients.

Among total arrhythmic events detected, five patients (45,45%) were previously (before the diagnosis of BrS) symptomatic while six patients (54,55%) were previously asymptomatic. There was no statistical difference between them as for the greater incidence of arrhythmic events in one group regarding the other one (p=0,914).

During follow-up, ILR recordings showed abrupt and significant variations of repolarization pattern compatible with dynamic Brugada pattern in six patients (17,65%), and one of them (the same with asymptomatic NSVT) was without previous evidence of altered ECG at baseline or during a febrile episode. No episodes of advanced atrio-ventricular blocks or atrial fibrillation or flutter were registered in our series.

TABLE 4. Description of ILR findings in our group during a mean follow-up of 17,76 months ± 13,41 SD

ILR findings	N=patients (%)
ILR symptoms driven recodrings (SDRs)	18 events
Patients with ILR symptoms driven recordings (SDRs)	7 (20,59%)
Non-clinically significant arrhythmias	5 (71,43%)
ST	4 (80%)
NSR	2 (40%)
SVEs	1 (20%)
Clinically significant arrhythmias (ventricular ARRH)	2 (28,57%)
Previously asymptomatic patient with ARRH	6 (31,58%)
Previously symptomatic patient with ARRH	5 (33,33%)
Implant to first SDR time	15,57 ± 16,65
Patients with dynamic Brugada pattern	6 (17,65%)
Total arrhythmias detected	11 (32,35%)
Symptomatic	7 (63,64%)
Asymptomatic	4 (36,36%)
Total arrhythmias detected	11 (32,35%)
Previously symptomatic patient	5 (45,45%)
Previously asymptomatic patient	6 (54,55%)
Patients without ARRH nor symptoms during FU	23 (67,65%)
LINQ artefacts	12 (35,29%)
FA (sinus arrhythmia)	7 (58,83%)
Pause (low QRS detection)	3 (24,50%)
VT (double counting QRS/T-wave)	2 (16,67%)
Complications (*end of ILR battery, peri-implantational hematoma, localized infection post-implant*)	2 (5,88%)
Therapy (DAI implantation)	2 (5,88%)

Values are n(%),mean ± DS or n.
Abbreviations: ILR: implantable loop recorder; SDR: symptoms driven recording; ST: sinus tachycardia; NSR: normal sinus rhythm; SVEs: supra-ventricular extrasystoles; ARRH: arrhythmias; FU: folloq-up; FA: atrial fibrillation.

8.5 Estimated risk of arrhythmic events

In order to perform the multivariate analysis by logistic regression, we took into account those variables that by literature and in the analysis of inference showed to be statistically significant and those that in spite of not being so, did evidence a certain tendency. However, we did not use the pre-syncope (p=0,142) and febrile seizures (p=0,035) variables because upon representing a really small portion of the sample, not converge in the multivariate analysis. The same happened with for f-QRS complex (p=0,048) and provocative test (p=0,152) variables. The induction of NSVT during EPS (p=0,009) was neither added for analysing because all patients showed arrhythmic events during the follow-up.

With none of the variables used to perform the analysis, we could obtain a significant p-value with a confidence interval of 95%. In contrast, the variables that showed to be statistically significant with a confidence interval of 90%, to present an incremented risk for arrhythmic events during follow-up were the presence of associated diseases, family SCD and QRS complex alteration.

In order to calculate the risk of having an arrhythmic event was used (RR adjusted – 1) x 100 (*Table 5*).

TABLE 5. Estimated risk[1] - relative risk raw and adjusted (95% confidence intervals) and their p-values of arrhythmic events in relation to selected covariates.

VARIABLES		RR raw (CI 95%)	p-value	RR adjusted (CI 95%)	p-value
Age[a]		0,944 (0,863-1,033)	0,258	0,934 (0,82-1,063)	0,292
Sex (female)		1,619 (0,727-3,606)	0,270	3,318 (0,871-12,643)	0,177
Abnormal basal ECG		2,333 (0,78-6,984)	0,216	6,310 (1,157-34,412)	0,131
Family SCD		2,743 (1,27-5,926)	**0,041****	5,222 (1,429-19,093)	**0,043****
Associated diseases		8,25 (2,366-28,765)	**0,043****	12,389 (2,604-58,94)	**0,042****
Symptomatic (syncope)		0,229 (0,071-0,732)	**0,098***	0,49 (0,077-3,114)	0,345
Basal ECG abnormal	Complete/incomplete RBBB	1,733 (0,811-3,704)	0,230	0,427 (0,12-1,525)	0,245
	PR interval prolongation	2,333 (0,779-6,984)	0,216	2,085 (0,473-9,192)	0,304
	QRS complex alteration	4,320 (1,935-9,647)	**0,032****	9,567 (2,073-44,173)	**0,043****

[1]According to multivariate logistic regression analysis.
Abbreviations: RR; Relative risk; ECG: electrocardiogram; SCD: sudden cardiac death; RBBB: right bundle branch block; f-QRS complex: fragmented QRS complex; EPS: electrophysiology study; NSVT: non-sustained ventricular tachycardia
[a]Mean (standard deviation).
**p<<0,1; **p<0,05*

9. DISCUSSION

To our knowledge, this is the only study that evaluates ILRs, exclusively in paediatric patients with BrS. There is one study performed with eleven adult BrS patients[41] and few data with pediatric patients with inherited arrhythmia syndromes[44]. Our study presents a cohort of thirty-four young patients with BrS without strict ICD implant indications in which a subcutaneous holter had implanted. We are completely aware of the no statistical signification of the obtained results due to the small sample size but there are some variables that has showed a certain tendency event though not being significant.

As we see above, our sample size is insufficient, which implies a reduced statistical power (54% in our case), that means, reduced probability of rejecting the null hypothesis when it is false (i.e. the estimators are effectively statistically significant). As we could not increase the size of the sample, we chose to increase the level of significance (alpha), which would lead to reduce the probability of committing type II error and, therefore, increasing the statistical power. In particular, we chose a level of significance equal to 10%.

As for the multivariate analysis, the presence of associated diseases (p=0,042), a family history of SCD (p=0,043) and the QRS complex alteration (p=0,043) were variables statistically significant which could increment the risk of suffering arrhythmic events, fact that coincide with current literature. However, a recent study by Sarkozy[59], among others, reported that a family history of SD in first-degree relatives or at a young age is not predictive for future arrhythmic events. But when it is associated with a spontaneous type 1 Brugada ECG pattern could increment the risk. In our cohort of the thirteen patients with family history of SCD, nine had a spontaneous ECG pattern (two of them type 1 pattern, three non-type 1 patterns, and four, Brugada pattern induced by fever). Therefore, only the four remaining patients showed a completely normal ECG pattern at baseline or with fever. There are studies that point out the risk associated with QRS complex alteration, especially, when it is fragmented as pointed Morita *et al.*[30].

In our study, the variables of age, presence of syncope and a complete/incomplete RBBB, seems to be a protective factor that reduce the risk of arrhythmic events (RR_a<1), although we have not found evidence that none of them has been statistically significant. Based on publications about BrS, we know

that is not like this, although not in our case. This lack of statistically significant results could be explained due to the small sample size studied.

It seems that being female has a risk > 200% of having arrhythmic events. The literature says the risk of having spontaneous arrhythmias is similar in children of both genders during the pediatric age. However, that risk increases after puberty only in male, due to their high levels of testosterone. For this reason, it is extremely important to perform systematically re-evaluations, especially in male during puberty, when the hormone starts to rise. Our results, possibly, are because a few girls were included in the study, who more than 50% suffered of arrhythmic events during the follow-up. Again, the results are not significant due to the insufficient sample. Likewise, the sex variable, abnormal ECG at baseline and PR interval prolongation variables showed a RR > 2 or > 100%, fact that implied that was necessary to control some confounding factors, effect called *residual counfounding*.

Finally, the variables that were excluded for the multivariate analysis, could be related with an incremented risk of arrhythmias, but due to an insufficient sample, in our study were not statistically significant. However, by bibliography, to have suffered an arrhythmogenic syncope or the induction of NSVT during EPS has been associated with an incremented risk (*section 3.11*).

As for ILR findings, during a mean follow-up of 17,76 months ± 13,41, a total of seven patients (63,64%) activated the LINQ's recording function due to symptom episodes, which in the majority of the cases (71,43%) were proved normal sinus rhythm/sinus tachycardia or minimal rhythm disturbances such as isolated supra-ventricular extrasystoles. Likewise, Kubala *et al.*[41] did not report any life-threatening ventricular arrhythmia, based on ILR data, as a cause of syncope in eight BrS patients after an average follow-up of 33 months or Avari Silvia JN *et al*.[44], when observing in their cohort of pediatric patients with inherited arrhythmia syndromes carriers of ILRs that the 90% of symptomatic transmissions were not associated with lethal arrhythmic events. Therefore, we could deduce that symptoms do not correlate well with the presence of lethal arrhythmic events and are not reliable markers for escalation of therapy or guidance around activity.

The use of the ILR to evaluate the aetiology of unexplained syncope in BrS patients was reported in a Canadian study[40] and in Giustetto *et al.*[5]. Distinguishing vasovagal mechanism from the dreaded ventricular arrhythmias is crucial in order to avoid ICD implant when it is not necessary (at least temporarily). In our group, ILRs were substantially helpful in avoiding it in five (71,43%) of our symptomatic patients. The same articles that point out the therapeutic effectiveness of ICD, highlight also its high frequency of complications and inappropriate shocks. For instance, Gonzalez *et al.*[52], Probst *et al*.[58] in FINGER BrS Registry or more recently Sacher *et al*[48], reported that rate of appropriate ICD shocks in patients with BrS after 39 months mean follow-up was lower in patients with history of syncope as compared with cardiac arrest survivals (0 vs 45%). For these reasons, the indication of an ICD is a difficult decision, especially in young patients that must be taken after a careful evaluation and only to proceed to device implantation only in those patients who really need it. When there is no clear indication of ICD, having a tool that allows continuous monitoring of the child's heart and, at least, delaying its placement, is a very useful strategy.

The ECG tracing identified episodes of non-sustained monomorphic ventricular tachycardia in two symptomatic patients (28,57%) manifested as syncope episodes. That involved a change in those patients' therapeutic management, requiring an early implantation of ICD. Especially in those cases, data provided by ILR was critically important in guiding their management. In the same line, Avari Silvia JN *et al*.[44] the ILR helped to change therapies in 30% of subjects.

Finally, automatic transmissions of subclinical arrhythmias by ILR in asymptomatic patients also had important consequences in their management. In our cohort, ILR recorded various episodes of asymptomatic NSVT in one patient who is being strictly followed with the aim of a prompt ICD implantation if needed. Other cases were the detection of asymptomatic episodes of abrupt repolarization changes, compatible with dynamic Brugada pattern, which could be a signal of uncontrolled fever, the need to introduce some medication, or insufficient quinidine titration. Those findings were in accordance with other studies[44] that found the 19% of automatically recorded transmission contained data that altered the patients' medical course.

10. IMPLANTABLE LOOP RECORDER LIMITATIONS

Artefacts were reported in twelve (35,29%) patients during follow-up, often related to misdetection of atrial fibrillation (due to significant sinus arrhythmia in children), and to double counting or under-detection of QRS and T waves during phases of signal alteration. However, those were easily recognized.

Two patients (5,88%) experienced device-related complications during follow-up. One of those, suffered from device infection a week after the procedure. The patient underwent re-implantation three months later without any further complications. In the other case, a peri-implantational hematoma appeared without infection. Finally, one patient ILR was replaced for a battery depletion after 29th months (*Table 4*).

11. STUDY LIMITATIONS

There are some potential limitations that should be considered:

- Brugada syndrome is considered a rare disease with a low prevalence among paediatric population, fact that led to have a relatively reduced number of patients. However, our study had performed in Arrhythmia Pediatric Unit of Sant Joan de Déu Hospital, a centre designed as coordinators of the European Reference Network in Rare Cardiac Diseases – subnetwork paediatrics. So, possibly patients regardless of their area of residence, came in order to be treated and followed there.
- A limitation from our study design was represented by its retrospective fashion which could have led to some recordkeeping and information biases.
- A non-probabilistic consecutive sampling method was used. Therefore, we tried to avoid the selection bia by including in the database only well-defined cases of patients who accomplished the inclusion and exclusion criteria.
- A small sample size and a brevity time of follow-up have been another limitation of our study, making difficult to draw statistically significant conclusions. However, we were able to identify a certain trend in some studied variables, which means, that a longer time of monitoring could

help to disclose further arrhythmic events and risk factors, especially when patients come to puberty.

- It is difficult to control confusion variables in observational studies, but we tried to minimize the possible bias ruling out all confusion factors known by an exhaustive bibliography research.
- Measurement biases could both appear during the process of registering some variables by the pertinent instrument and upon interpreting the results. In order to minimize them, all instruments were calibrated periodically and each result was analysed at least by two expert paediatric cardiologists in the syndrome. In case of discrepancy, the results were evaluated by a third expert.
- Due to the anonymization of the process, any significant rhythm disturbance that could demand a treatment, we could not contact directly to the anonymous patient. However, those were followed closely by their reference paediatric cardiologist, responsible for reviewing the ILR's recorded data and took the appropriate measures based on its findings.
- Although we knew that using a multivariate COX model would have been ideal, we did not get the different moments when arrhythmic events appeared. For the same reason, we neither could calculate the incidence rate of arrhythmic events using the Poisson model. So, we finally used a regression logistic model and calculated the incidence as a proportion with its IC 95%.
- ILR are compatible with total body nuclear magnetic resonance imaging (MRI), although in cardiac MRI they could cause significant intensity artefacts in diagnostic images as well as these could be mistaken for a tachyarrhythmia in the ECG. Therefore, it is important to take this into account upon interpreting an ECG. Also, further investigation about MRI techniques is required in order to eliminate imaging artefacts.

12. CONCLUSIONS

The purpose of our study was to prove the effectiveness of ILRs in order to detect arrhythmic events in patients with non-high-risk BrS, considering it as a useful tool for guiding their management.

This study summarizes a single-experience with 34 patients with Brugada syndrome that received an ILR at an age of < 21 years. After a mean follow-up of 18 months the ILR contributed to detect arrhythmic events in patients with Brugada syndrome, confirming our main hypothesis. The ILR was determinant in order to exclude ventricular arrhythmias as a cause symptoms in 71,43% of symptomatic patients. In general, the device was crucial in decision making regarding ICD implant in 81,82% of patients, both symptomatic and asymptomatic, who ILR detected arrhythmias (8 avoided implants and one potential implant in one asymptomatic patient). Especially important, the ILR allowed to detect ventricular arrhythmias in two symptomatic patients, leading to a change in their therapeutic management, requiring an early implantation of ICD.

As a conclusion, the implantable loop recorder allows a long-term continue monitoring of heart rhythm in patients with increased risk of life-threatening arrhythmias allowing to detect the best moment for ICD implantation. So, the device should be considered as a tool for clinical management of paediatric patients with non-high-risk BrS and other inherited arrhythmic diseases. Long-term follow-up studies are needed to add more information in this field.

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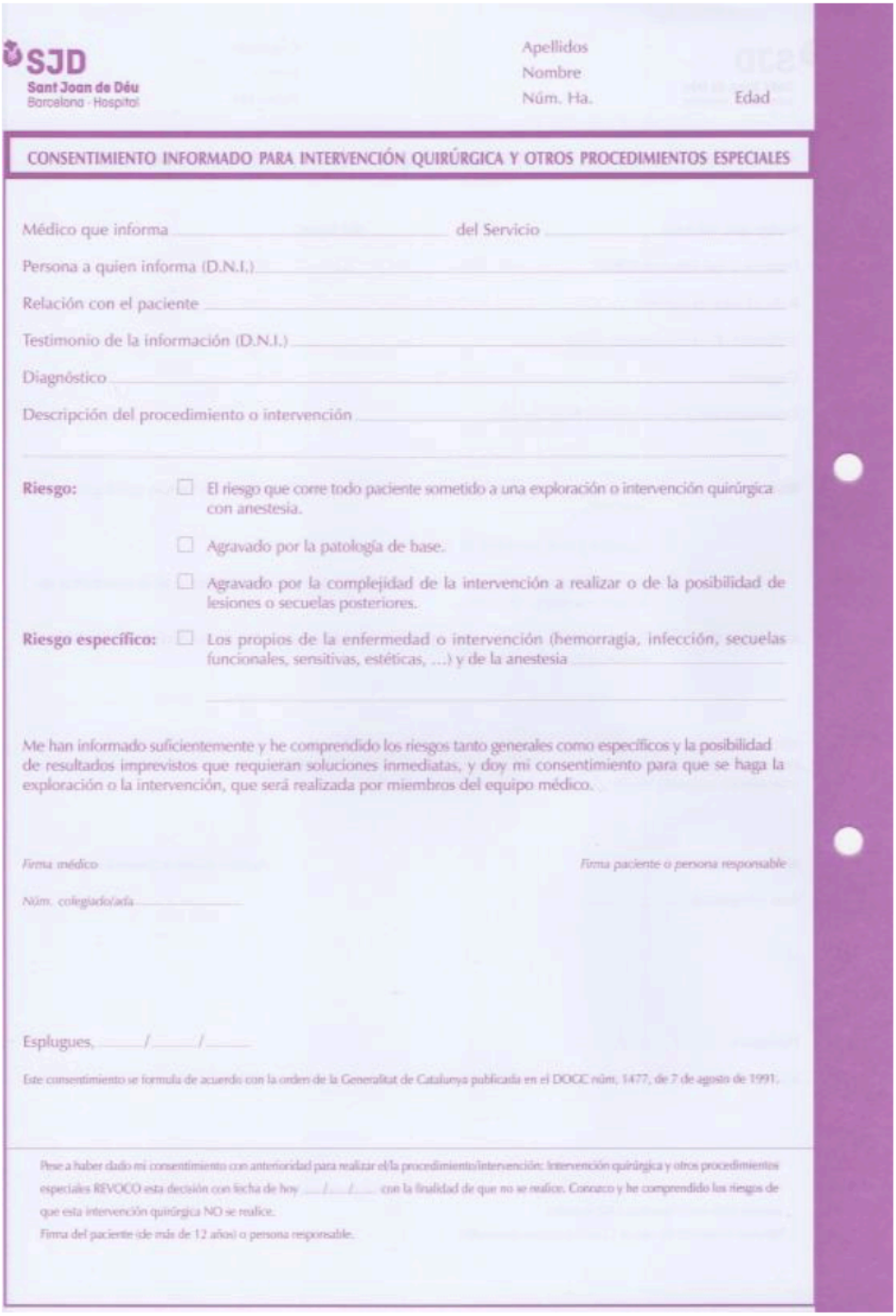
14. ANNEXES

14.1 Annex I: Informed consent for invasive procedures (in Catalan and in Spanish)



SJD
Sant Joan de Déu
Barcelona · Hospital

Apellidos
Nombre
Núm. Ha. Edad

CONSENTIMIENTO INFORMADO PARA INTERVENCIÓN QUIRÚRGICA Y OTROS PROCEDIMIENTOS ESPECIALES

Médico que informa _____ del Servicio _____

Persona a quien informa (D.N.I.) _____

Relación con el paciente _____

Testimonio de la información (D.N.I.) _____

Diagnóstico _____

Descripción del procedimiento o intervención _____

Riesgo:
- ☐ El riesgo que corre todo paciente sometido a una exploración o intervención quirúrgica con anestesia.
- ☐ Agravado por la patología de base.
- ☐ Agravado por la complejidad de la intervención a realizar o de la posibilidad de lesiones o secuelas posteriores.

Riesgo específico:
- ☐ Los propios de la enfermedad o intervención (hemorragia, infección, secuelas funcionales, sensitivas, estéticas, ...) y de la anestesia _____

Me han informado suficientemente y he comprendido los riesgos tanto generales como específicos y la posibilidad de resultados imprevistos que requieran soluciones inmediatas, y doy mi consentimiento para que se haga la exploración o la intervención, que será realizada por miembros del equipo médico.

Firma médico *Firma paciente o persona responsable*

Núm. colegiado/ada

Esplugues, ____/____/____

Este consentimiento se formula de acuerdo con la orden de la Generalitat de Catalunya publicada en el DOGC núm. 1477, de 7 de agosto de 1991.

Pese a haber dado mi consentimiento con anterioridad para realizar el/la procedimiento/intervención: Intervención quirúrgica y otros procedimientos especiales REVOCO esta decisión con fecha de hoy ____/____/____ con la finalidad de que no se realice. Conozco y he comprendido los riesgos de que esta intervención quirúrgica NO se realice.

Firma del paciente (de más de 12 años) o persona responsable.

SJD
Sant Joan de Déu
Barcelona · Hospital

Cognoms
Nom
Núm. Ha. Edat

CONSENTIMENT INFORMAT PER A INTERVENCIÓ QUIRÚRGICA I ALTRES PROCEDIMENTS ESPECIALS

Metge que informa _____ del Servei _____

Persona a qui informa (DNI) _____

Relació amb el pacient _____

Testimoni de la informació (DNI) _____

Diagnòstic _____

Descripció del procediment o intervenció _____

Risc:
- ☐ El risc que té tot pacient que és sotmès a una exploració o intervenció quirúrgica amb anestèsia.
- ☐ Agreujat per la patologia de base.
- ☐ Agreujat per la complexitat de la intervenció que s'ha de realitzar o de la possibilitat de lesions o seqüeles posteriors.

Risc específic:
- ☐ Els propis de la malaltia o intervenció (hemorràgia, infecció, seqüeles funcionals, sensitives, estètiques, ...) i de l'anestèsia _____

M'han informat suficientment i he comprès els riscs tant generals com específics i la possibilitat de resultats imprevistos que requereixin solucions immediates, i dono el meu consentiment perquè es faci l'exploració o la intervenció, que serà realitzada per membres de l'equip mèdic.

Signatura metge/essa *Signatura pacient o persona responsable*

Núm. col·legiat/ada _____

Esplugues, ____/____/____

Aquest consentiment es formula d'acord amb l'ordre de la Generalitat de Catalunya publicada al DOGC núm. 1477, de 7 d'agost de 1991.

Tot i haver donat el meu consentiment amb anterioritat per realitzar el/la procediment/intervenció: Intervenció quirúrgica i altres procediments especials REVOCO aquesta decisió amb data d'avui ____/____/____ amb la finalitat de que no es realitzi. Conec/o i he comprès els riscos de que aquesta intervenció quirúrgica NO es realitzi.

Signatura del pacient (de més de 12 anys) o persona responsable.

Mod. 1118.-B

14.2 Annex II: CEIC's authorization

Fundació Sant Joan de Déu

CEIC Fundació Sant Joan de Déu

Informe Dictamen Favorable
Proyecto Investigación Biomédica
C.I. PIC-169-17
20 de diciembre de 2017

Dr. Pau Ferrer Salvans
Secretario del CEIC Fundació Sant Joan de Déu

CERTIFICA

1º. Que el CEIC Fundació Sant Joan de Déu en su reunión del día 18/12/2017, ha evaluado la propuesta del promotor referida al estudio:
Título: "Síndrome de Brugada en niños"
Código Interno: PIC-169-17
IP: Georgia Sarquella Brugada

Considera que:

- El proyecto se plantea siguiendo los requisitos de la Ley 14/2007, de 3 de julio, de Investigación Biomédica y su realización es pertinente.
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- Son adecuados tanto el procedimiento para obtener el consentimiento informado como la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el estudio.
- El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.
- La capacidad de los investigadores y los medios disponibles son apropiados para llevar a cabo el estudio.

2º. Por lo que este CEIC emite un **DICTAMEN FAVORABLE.**

3º. Este CEIC acepta que dicho estudio sea realizado en los siguientes CEIC/Centros por los Investigadores:

- **HOSPITAL SANT JOAN DE DÉU. Georgia Sarquella Brugada.**

Lo que firmo en Esplugues de Llobregat, a 20 de diciembre de 2017

Fdo:

Fundació Sant Joan de Déu

Dr. Pau Ferrer Salvans
Secretario del CEIC Fundació Sant Joan de Déu

Edifici Docent Sant Joan de Déu - c. Santa Rosa, 39-57, 3a planta, 08950 Esplugues de Llobregat / Barcelona
Telèfon + 34 93 600 97 51 - Fax + 34 93 600 97 71 e-mail: info@fsjd.org web: www.fsjd.org

14.3 Annex III: Implantable loop recorder protocol

Sant Joan de Déu
Barcelona · Hospital

Barcelona, 1 de diciembre de 2017

Protocolo de Implante de Holter subcutáneo

Previo al implante:

- El paciente tiene indicación de implante de holter subcutáneo.
- El paciente ha recibido la información sobre el procedimiento, las indicaciones y las posibles complicaciones.
- El paciente ha firmado el consentimiento informado.

La secretaria de cardiología contacta con el paciente y le indica:

- Día y hora de ingreso en la Sala Arco Iris (primera planta de Consultas Externas)
- Ayunas de 6 horas

Se programa ingreso ambulatorio, sin reserva de cama (si el implante es el único procedimiento). Si el implante de holter subcutáneo se hace simultáneamente a otro procedimiento, seguirá el protocolo de ingreso según necesidades.

En la Sala Arco Iris se le coloca Lidocaina 1% en crema en la región mediotorácica submamaria izquierda 1 hora antes de la hora del procedimiento. Se coloca un apósito trasparente impermeable para cubrir la crema.

El camillero de cardiología (Busca 80030) sube al paciente acompañado de sus padres a la sala de electrofisiología. Salvo excepciones, no precisa silla ni camilla.

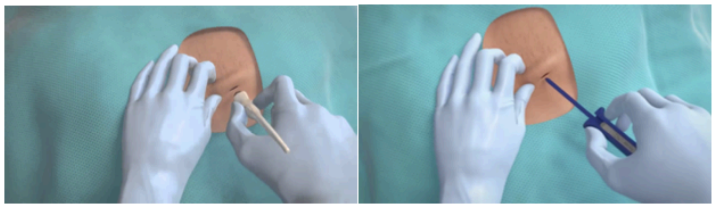
En antesala de electrofisiología se evalúa el grado de estrés y madurez del paciente.

- Si el paciente es colaborador se puede plantear un procedimiento sin sedación. En todo caso, se le explica de nuevo al paciente todo el protocolo que se le realizará.
- Si se prevé que el paciente no colaborará, se coloca una vía periférica y se administra leve sedación intravenosa en presencia de los padres.

El paciente entra a la sala de electrofisiología. Según criterio del anestesista, puede entrar acompañado de uno de los progenitores (que deberá vestirse adecuadamente con mono verde de un solo uso).

Procedimiento de inserción del holter subcutáneo:

- Administración de anestesia subcutánea: Lidocaina 5% 4,5ml + Bupivacaina 0,5% 4,5ml + bicarbonato 1M 1ml en la región mediotorácica submamaria izquierda. Masajear la zona.
- Inserción del holter subcutaneo mediante el kit de inserción del paquete.
- Cierre por aproximación con pegamento quirúrgico (Dermabond).
- Colocación de apósito poroso



Programación del dispositivo mediante aplicación o interrogador.

Activación del sistema de monitorización remota y formación de la familia para el uso del sistema domiciliario.

Alta en la página web de monitorización remota.

Unidad de Arritmias

Georgia Sarquella-Brugada
Sergi Cesar

14.3 Annex IV: Summary of patient characteristics

TABLE 1. Clinical, electrocardiogram and electrophysiological characteristics of patients included in the study

WN° PATIENT	AGE	SEX	REASON FOR EVALUATION	FAMILY SCD	SCN5A MUTATION POSITIVE	SYMPTOMS (PREVIOUS TO DX)	SPONT. TYPE 1 BR PATTERN	BR PATTERN WITH FEVER	BR PATTERN WITH AJ/F TEST	ECG CHARACTERISTICS	EPS CHARACTERISTICS	ASSOCIATED DISEASES
1	16	M	Fam S	+	- (HCN4)	-	-	-	+	Incomplete RBBB QRS 114ms	-	-
2	19	M	Fam S	+	+	-	-	-	+	No abnormalities	-	-
3	6	M	Fam S	+	+	-	-	+	+	Complete RBBB QRS 134ms PR 182ms	HV 56ms	-
4	16	M	Fam S	+	+	-	-	-	+	Incomplete RBBB QRS 119ms PR 185ms	AH 125ms	-
5	4	F	Fam S	+	-	Febrile seizures	-	+	+	Incomplete RBBB	-	-
6	6	F	Fam S	-	+	Syncope	-	-	+	Incomplete RBBB	-	-
7	5	M	Fam S	-	+	Syncope	-	+	+	No abnormalities	-	-
8	7	F	Fam S	-	+	-	-	+	+	Incomplete RBBB	-	-
9	13	M	Fam S	-	NOT DONE	Nocturnal awakenings	-	+	+	No abnormalities	HV 56ms	-
10	8	M	Suspicious ECG	-	- (CACNA2D1)	-	-	+	+	Mild ST-elevation (V_1) PR 160ms	NSVT	-
11	9	M	Fam S	-	NOT DONE	Pre-syncope	-	+	+	Incomplete RBBB QRS 120ms	-	-
12	14	M	Fam S	-	+	-	-	+	+	Incomplete RBBB. Negative T-waves (V_6) and isodiphasic (V_5)	-	-
13	11	M	Fam S	-	+	-	-	-	+	Complete RBBB QRS 122ms	VRP < 200ms	-
14	12	M	Suspicious ECG	-	- (ABCC9)	Chest pain during fever	-	+	+	Incomplete RBBB	VRP < 200ms	Attention disorder
15	14	M	Fam S	-	+	Syncope	-	+	+	Left axis deviation PR 185ms	AH 165ms VRP < 200ms	-
16	12	F	Fam S	-	-	-	-	-	+	No abnormalities	VRP < 200ms	-
17	17	M	Fam S	+	- (HCN4)	-	-	-	+	Early repolarization pattern Short QTc (360ms)	VRP < 200ms	-
18	9	M	Symptoms	-	-	Syncope	-	UNKNOWN	+	Incomplete RBBB	-	-
19	8	M	Fam S	+	- (PKP2)	-	-	+	+	No abnormalities	-	-
20	16	M	Fam S	-	NOT DONE		-	UNKNOWN	-	Complete RBBB, f-QRS (V_2-V_2) QRS 138ms Sinusal and AV disfunction (asystole 5seg)	NSVT	Suspicious of Lev Lenegre syndrome
21	8	F	Fam S	-	-		-	UNKNOWN	+	No abnormalities	AH 124ms	-
22	6	M	Fam S	+	- (SCN1A)	Febrile seizures	-	+	-	No abnormalities	NSVT	-
23	7	M	Symptoms	-	NOT DONE	Syncope	-	UNKNOWN	+	No abnormalities	-	-
24	13	F	Fam S	+	- (MYH6; MYH7)		- (type 2)	UNKNOWN	+	No abnormalities	-	-
25	9	F	Fam S	+	+	-	- (type 2)	+	+	Q wave (DIII/aVF) QRS 188ms	VRP < 200ms	-
26	4	F	Symptoms	-	-	Syncope	+	+	NOT DONE	f-QRS (V_1)	VRP < 200ms	Autism + growing retard (Rett syndrome)
27	16	F	Fam S	+	NOT DONE	-	+	+	NOT DONE	f-QRS (DIII)	VRP < 200ms	-
28	12	M	Suspicious ECG	-	-	Chest pain during fever	- (type 2)	+	+	No abnormalities	VRP < 200ms	-
29	12	M	Fam S	-	NOT DONE	-	+	UNKNOWN	+	QRS 112ms	VRP < 200ms NSVT	-
30	13	M	Suspicious ECG	-	-	Atypical chest pain	- (type 2)	-	+	Complete RBBB f-QRS (V_1-V_3) QRS 118ms.	HV 58ms VRP < 200ms	-
31	4	F	Fam S	+	+	-	+	UNKNOWN	+	Complete RBBB, f-QRS (V_1) QRS 132ms	HV 64ms	Sequelae of anoxic-ischemic encephalopathy
32	11	M	Symptoms	-	+	Syncope	- (type 2)	UNKNOWN	+	Complete RBBB QRS 150ms	HV 60ms	-
33	15	M	Symptoms	-	+ (CSRP3 +)	Syncope	+	UNKNOWN	NOT DONE	No abnormalities	AH 128ms	-
34	5	M	Fam S	+	-		- (type 2)	-	+	No abnormalities	-	-

SCD: sudden cardiac death; AjF: ajmaline, flecainide; ECG: electrocardiogram; EPS: electrophysiological study; Fam S: familial screening; RBBB: right bundle branch block; LBBB: left bundle branch block; QRS complex on ECG; PR interval on ECG; f-QRS: fragmented QRS complex; QTc: corrected QT; short QT: short QT syndrome; AH: atrio-His interval time on ECG; HV: His-ventricular interval time on ECG; VRP: ventricular refractory period; DAI: implantable cardioverter defibrillator; SCN5A+: positive mutation for the gene encoding the subunit SCN5A of sodium channel

14.4. Annex V: Summary of ILR findings

TABLE 2. Report of symptoms driven recording and ILR findings during follow-up

Nº PATIENT	AGE AT ILR IMPLANT	FOLLOW-UP (MONTHS)	SYMPT. DELAY FROM IMPLANT (MONTHS)	SYMPTOMS (Nº EPISODES) AND ILR FINDINGS	LINQ BR PATTERN	VENTRICULAR ARRH	OTHER ARRHYTHMIAS	ILR ARTIFACTS/ OTHER	THERAPY
1	15	9	-	-	-	-	-	-	
2	16	44	-	-	+	NSVT	SB, VEs, paroxysmal ST	AF (sinus arrhythmia)	
3	5	20	-	-	-	-	-	-	
4	12	38	11, 15, 20	Palpitations (3) during ST	-	-	-	End of battery 03/2018	
5	1	38	-	-	-		Paroxysmal SVT	Pauses (low QRS detection)	
6	3	38	-	-	-	-	-	VT/SVT (double counting QRS/T waves)	
7	2	29	-	-	-	-	-	-	
8	5	24	-	-	-	-	-	VT (double counting QRS/T waves)	
9	12	17	-	-	-	-	-	AF (sinus arrhythmia)	
10	6	18	-	-	+	-	-	AF (sinus arrhythmia)	
11	8	12	1, 1, 3	Pre-syncope (3) during ST	-	-	-	-	
12	13	11	-	-	-	-	-	-	
13	9	24	-	-	-	-	-	Pauses (low QRS detection)	
14	1	21	-	-	-	-	-	-	
15	13	13	-	-	-	-	-	-	
16	11	12	-	-	-	-	-	Post-implant localized infection	
17	16	9	-	-	-	-	-	-	
18	9	3	-	-	-	-	-	-	
19	7	3	-	-	-	-	-	-	
20	13	45	43	Syncope (3) during NSTV	-	-	-	Hematoma peri-implantational LINQ (no infected)	DAI
21	8	3	-	-	-	-	-	Pauses (low QRS detection)	
22	3	40	40	Syncope (1) during FV	-	-	-	LINQ removal (07/2018)	DAI
23	6	3	-	-	-	-	-	-	
24	13	3	-	-	-	-	-	-	
25	6	33	4, 23, 24	Pre-syncope (3): 1 during ST, 2 during NSR	+	-	-	AF (sinus arrhythmia)	
26	3	21	5	Febrile seizures (1) during ST	+	-	-	-	
27	15	18	-	-	-	-	-	-	
28	10	18	-	-	-	-	-	-	
29	11	15	-	-	-	-	-	AF (sinus arrhythmia)	
30	12	10	5, 7, 7, 8	Pre-syncope (2) during NRS Palpitations (2) during SVEs	-	-	-	-	
31	2	3	-	-	+	-	-	AF (sinus arrhythmia)	
32	11	3	-	-	-	-	-	-	
33	13	3	-	-	-	-	-	-	
34	4	3	-	-	-	-	-	AF (sinus arrhythmia)	

ILR: Implantable loop recorder; ARRH: arrhythmias; NSR: normal sinus rhythm; NSVT: non-sustained ventricular tachycardia; SB: sinus bradycardia; ST: sinus tachycardia; SVE: supra-ventricular extrasystole; SVT: supra-ventricular tachycardia; VE: ventricular extrasystole; AF: atrial fibrillation; DAI: Imblantable cardioverter defibrillator

14.5 Annex VI: ECG tracing of ILR

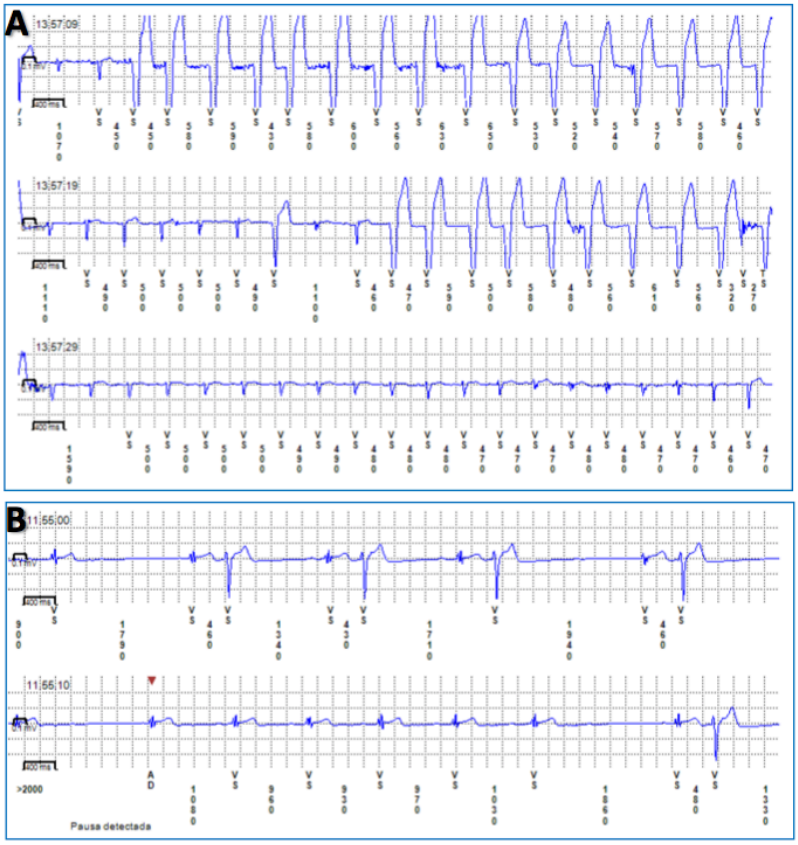


FIGURE 9: *Patient who ILR report of slow non-sustained asymptomatic ventricular tachycardia (A). ILR report of an episode of sinus bradycardia with a longest pause of 1860 msec. and ventricular escape rhythm (B).*

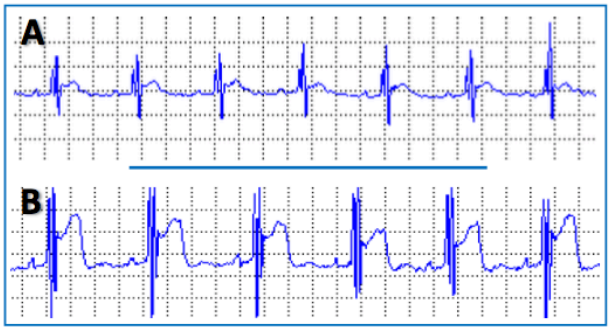


FIGURE 10. *Normal sinus rhythm (A). ILR record of abrupt repolarization change registered the same day compatible with dynamic Brugada pattern (B).*

14.6 Annex VII: Levels of evidence in therapeutic studies

Level	Type of evidence
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	"Outcomes" research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case-control study
5	Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles"

Levels of evidence for therapeutic studies, extracted from the Center for Evidence-Based Medicine