

## Brugada Phenocopy Emerging as a New Concept. Response

### Fenocopia de Brugada: surgimiento de un nuevo concepto. Respuesta

#### To the Editor,

The authors appreciate the interest in the case report we published in *Revista Española de Cardiología* concerning the observation of the Brugada electrocardiographic (ECG) pattern in a patient with hyperkalemia.<sup>1</sup> We likewise welcome the introduction of the concept of phenocopy, an expression with which our finding is compatible.<sup>2,3</sup> We also consider it opportune to stress that both the latest consensus on ECG diagnosis of Brugada syndrome and the introduction of the term *phenocopy* are more recent than the online publication of our case report in 2011.<sup>2-4</sup> The definitions of the ECG patterns that are typical of Brugada syndrome and those that mimic this syndrome in the presence of serum electrolyte disturbances were introduced subsequent to our publication.

It is important to highlight reasons for attributing the changes observed in the ECG to hyperkalemia rather than to the acidosis and hyponatremia also observed in our patient. Reports of Brugada phenocopy associated with hyponatremia and acidosis have described the development of pseudo J waves in the QRS complex and ST segment depression in leads other than right precordial leads. These are precisely the features that differentiate this ECG pattern from type 1 Brugada pattern.<sup>5,6</sup> Other possible causes (hyperglycemia, drugs, fever, and myocardial ischemia) were ruled out in the case discussed in our report.

We appreciate any contribution that aids in the understanding of the mechanisms involved in the induction of ECG patterns mimicking Brugada syndrome (phenocopies) and other patterns, such as early repolarization, which can also be associated with the risk of sudden cardiac death.<sup>7</sup>

Finally, we agree with Dr. Anselm on the importance of performing a challenge test with flecainide to rule out Brugada syndrome. Until the prognosis of patients presenting with

Brugada phenocopy has been established, it is advisable to perform pharmacological challenge tests and, if appropriate, to induce ventricular arrhythmias by means of an electrophysiological study.

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## RASopathies: From Noonan to LEOPARD Syndrome

### RASopatías: del síndrome de Noonan al síndrome LEOPARD

#### To the Editor,

We have read with interest the article recently published by Carcavilla et al.<sup>1</sup> titled "LEOPARD Syndrome: A Variant of Noonan Syndrome Strongly Associated With Hypertrophic Cardiomyopathy." However, we would like to add some comments that we find interesting.

LEOPARD syndrome (LS) (OMIM 151100) and Noonan syndrome (NS) (OMIM 163950) are two disorders that are part of a newly classified family of autosomal dominant syndromes termed "RASopathies", which are caused by germline mutations in components of the RAS-MAPK (mitogen-activated protein kinases) signal transduction pathway<sup>2</sup> that is involved in the regulation of normal cell proliferation, survival, and differentiation.

Although the diagnosis of LS is made on clinical grounds by observation of key features, none of which is pathognomonic, to provide a valid overview on symptoms and features of LS we should not overestimate the reports published in the pre-molecular era, because these cohorts may consist of heterogeneous diseases. In fact, in early childhood the phenotype of LS can be typical of NS;

however, with age other characteristic features of LS, including lentigines, hypertrophic cardiomyopathy (HCM), and hearing loss, may appear. For this reason, anomalies observed in molecularly confirmed cases should be regarded as more reliable.

Genetically, both syndromes share mutations in the *PTPN11* (protein-tyrosine phosphatase, non-receptor type 11) gene on chromosome 12q24, as they are heterozygous missense mutations in *PTPN11* observed in up to 90% and 50% of LS and NS cases, respectively. Similarly, mutations in the *RAF1* (v-Raf-1 murine leukemia viral oncogene homolog 1) gene on chromosome 3p25.2 and mutation in the *BRAF* (v-Raf murine sarcoma viral oncogene homolog B1) gene on chromosome 7q34 are also seen. However, the point mutations identified in *PTPN11* that are associated with NS are distinct from those associated with LS and therefore with different biochemical properties: gain-of-function mutations in *PTPN11* are more frequent in NS patients<sup>3,4</sup> while a loss-of-function or dominant-negative mutations in *PTPN11* are more prevalent in patients with LS.<sup>5,6</sup> These gain-of-function and loss-of-function mutations may explain the differences in phenotypes between these two syndromes.

Although it is not included in the LEOPARD acronym, HCM is the most frequent anomaly observed, representing a potentially life-threatening problem in these patients. HCM, which is generally

asymmetric and progressive and commonly involves the intraventricular septum, is detected in up to 80% of patients with a cardiac defect and may associate with significant left ventricular outflow tract obstruction in up to 40% of cases<sup>7,8</sup>. Although treatment algorithms are similar between LS patients with ventricular hypertrophy and patients with familial HCM, without an evidence-based diagnosis, despite their analogous character it is clear that the pathophysiology and dynamics of HCM in LS differ from ventricular hypertrophy of other causes. On the contrary, the most common cardiac manifestation in NS is pulmonic stenosis resulting from dysplastic valve leaflets, followed (less frequently) by HCM, mitral stenosis, and atrial, ventricular and atrioventricular septal defects, or (rarely) by double outlet right ventricle.

To date, it is unclear whether the genotype may influence the clinical course in LS patients with HCM, especially because many of the affected individuals described in the literature are children and no clear risk figures based on a follow-up patient cohort study of a sufficient size is available. However, anecdotal reports provide enough evidence to state that long-term prognosis seems benign in LS patients with only mild cardiac abnormalities, whereas HCM in LS is indeed associated with a risk of fatal cardiac events as seen in primary HCM<sup>9</sup>.

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## New Oral Anticoagulants in Nonvalvular Atrial Fibrillation: Findings and Implications of the ROCKET Study

### Nuevos anticoagulantes orales en fibrilación auricular no valvular: resultados e implicaciones del estudio ROCKET

#### To the Editor,

With respect to the article "Findings and Implications of the ROCKET Study,"<sup>1</sup> we are in agreement with López-Sendón et al. that the findings<sup>2</sup> support the decision of the health authorities to grant authorization of rivaroxaban,<sup>3,4</sup> and that these results could help change stroke and systemic embolism prevention strategies in patients with atrial fibrillation, given that the new oral anticoagulants represent a major therapeutic advance. However, several aspects are of particular importance when assessing the clinical implications of the ROCKET study, and these deserve special attention.

The first is related to the efficacy of rivaroxaban vs warfarin. On this point, we have detected a contradiction in the text. In the section "Findings of the ROCKET Study," the authors state that there were no significant differences in the efficacy endpoint in the intent-to-treat analysis, whereas in the section "Clinical Implications of the ROCKET Study," they state that, cost permitting, the new anticoagulants should displace warfarin in the prevention of stroke in patients with atrial fibrillation in most cases, given their greater efficacy and ease of administration. In our opinion, regardless of the associated costs, this latter statement is incongruent given that rivaroxaban was not shown to be superior to warfarin.

Regarding the bleeding complications, we agree with the authors that rivaroxaban does not increase the risk of serious or

clinically relevant bleeding compared to warfarin and significantly decreases intracranial and fatal bleeding. However, we find no allusion to the increase in severe gastrointestinal bleeding in the group treated with rivaroxaban compared to warfarin (odds ratio=1.60; 95% confidence interval, 1.29-1.98).<sup>5</sup>

Moreover, although it is true that the new oral anticoagulants represent major progress in medical treatment, we should nevertheless be aware of their limitations. In fact, although the lack of need for monitoring is considered an advantage, lack of follow-up could negatively affect adherence to treatment. In view of the short half-lives of these drugs, this aspect is of particular importance, as missed doses may quickly have an effect on the efficacy of treatment.<sup>6</sup> Poor adherence could cancel out the potential clinical benefit of new oral anticoagulants compared to vitamin K antagonists and even increase the risk of stroke or systemic embolism. As observed in the ROCKET study, patients who discontinued treatment with rivaroxaban had a higher incidence of stroke or systemic embolism compared to those who discontinued warfarin.<sup>2</sup> Likewise, other limitations, in no way insignificant, for the use of new oral anticoagulants are the lack of a specific antidote to reverse their effect and the limited experience in the management of bleeding complications in patients treated with these drugs.<sup>7</sup> Finally, as with any other new drug, the available safety information is currently limited.

Thus, we do not agree with the authors when they state that the new oral anticoagulants should replace warfarin in most cases if costs allow. It is clear that the direct cost of treatment with new anticoagulants is markedly greater than treatment with vitamin K antagonists.<sup>8</sup> However, economic motives are not the only reasons for caution in the use of these drugs, as there are also important aspects related to efficacy that are worthy of consideration.