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Autoimmunity and cardiac arrhythmias in endemic pemphigus foliaceus—Association, correlation, or causation?

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The most essential effector mechanism of the immune system is to eliminate a variety of pathogens while yet maintaining a delicate balance between immune responses and self-tolerance. Although a low level of autoreactivity is physiologic and essential to form and maintain the normal immune repertoire, when the mechanisms of self-tolerance breaks down or fails (ie, autoimmunity), autoimmune disease can occur. Autoimmunity can result from a variety or combination of mechanisms including genetic susceptibility, environmental triggers or failure of natural tolerance mechanisms. Epidemiological studies indicate that autoimmune disorders affect approximately 5% of the populations of Western countries, and their incidence is also on the rise globally.^{1,2}

Autoimmunity is known to be associated with cardiovascular diseases, including cardiac arrhythmias.³ Large population studies have shown that the risk of atrial fibrillation is significantly increased in patients with celiac disease,⁴ psoriasis,⁵ and rheumatoid arthritis.⁶ The presence of activating anti- β_1 -adrenergic receptor autoantibodies has been reported to cause inappropriate sinus tachycardias, atrial tachycardias, and cardiomyopathy.⁷ More importantly, several arrhythmogenic autoantibodies targeting specific calcium, sodium, and potassium channels in the heart have been identified.⁸ Such autoimmune cardiac channelopathies are best exemplified by the congenital complete heart block in patients with lupus erythematosus caused by inhibition of fetal L-type calcium channels by maternal anti-Ro/SSA antibodies.⁸

In this issue of **HeartRhythm**, Abreu-Velez et al⁹ report cardiac rhythm abnormalities in patients affected by endemic pemphigus foliaceus in El Bagre, Colombia (El Bagre-EPF). One-third of these patients were found to have autoimmune reactivity against the heart.¹⁰ In this study, 30 patients with El Bagre-EPF were compared with 30 controls from the endemic area matched by sex, age, weight, work, comorbidities, and exposure to chemicals. Patients with El Bagre-EPF were found to have a significantly higher prevalence of sinus bradycardia and conduction system abnormalities, including left bundle branch block, left anterior fascicular block, and left posterior fascicular block. Immunohistochemical studies demonstrated the presence of autoantibodies in the adherens junctions in nodal cells, His bundle, and cardiac conduction system. An autoimmune mechanism is implicated in the development of cardiac rhythm disturbances in patients with El Bagre-EPF.

There are several interesting features of the Abreu-Velez study. First, most autoimmune diseases are nonendemic but El Bagre-EPF is a variant of endemic pemphigus foliaceus, mainly confined to a small municipality in Colombia. This condition frequently occurs in families, suggesting a possible mechanism involving gene-environment interaction. Second, as a diagnostic criteria for this condition, autoantibodies against desmoglein 1 and desmoplakins are present in these patients. These are integral proteins of desmosomal structures, although different isoforms are present in skin and cardiomyocytes. Loss-of-function mutations of desmosomal proteins are known to be associated with the development of cardiomyopathy and arrhythmogenesis.^{11,12} Indeed, patients with pemphigus have been found to have increased cardiovascular mortality.¹³ Third, despite the challenges associated with the availability of local infrastructure for scientific investigation, the authors were able to obtain 7 autopsy hearts and electrocardiograms from 30 patients with El Bagre-EPF with 30 matched controls. This basic medical and scientific information provided some rudimentary insights into potential cardiac disease processes in this condition. Fourth, using several different immunological techniques including direct and indirect immunofluorescence, confocal microscopy, and immunohistochemistry, sera from about one-third of the patients with El Bagre-EPF showed positive staining to the sinus node, atrioventricular node, or His bundle in cow heart preparations. These findings provide some pathophysiological support for the electrocardiographic findings involving sinus node and conduction system abnormalities in patients with El Bagre-EPF.

However, significant limitations exist in the present study. First, the design of the matching was unclear; the wide exposure distribution raises the potential concern for selection bias. Moreover, the sample size was rather small and may limit generality. The study is further hampered by the lack of detailed information on the cardiovascular comorbidities and cause of death in subjects. Establishment of a registry of this condition would be a critical component of future efforts. Second, the electrocardiographic findings in the subjects are relatively modest: mainly sinus bradycardia and conduction system abnormalities in the form of left bundle branch block and fascicular blocks. These conditions are common in the general population without autoimmune diseases or pemphigus foliaceus. In addition, none of the patients with electrocardiographic findings had symptoms, raising the question about the clinical significance of the findings.

Third, the findings of this study are correlative in nature and not causative in mechanism. Colocalization of immunoreactivity between sera from patients with El Bagre-EPF and commercial antibodies, such as that against MYZAP, is used to assess potential associations on cell signaling mechanisms. Such speculations, however, may be premature. In comparison, the establishment of autoimmune mechanisms associated with anti- β_1 -adrenergic receptor antibodies includes not just the presence of such autoantibodies in patients with heart failure but also the identification of the second extracellular loop of the β_1 -adrenergic receptor as the site of receptor activation by autoantibody. In addition, inbred rats immunized against this loop of receptor peptide produced β_1 -adrenergic receptor stimulating antibodies followed by development of heart failure. In addition, transfer of sera from immunized rats to healthy animals of the same strain reproduced the cardiomyopathy pheno-type.^{7,14} Similarly, the role of anti-Ro/SSA antibodies in the development of congenital complete heart block is supported by a substantial body of direct evidence that

include inhibition of L-type calcium currents by anti-Ro/SSA antibodies and induction of atrioventricular block in isolated animal hearts by exposure to autoantibodies isolated from patients. In addition, animals immunized with the recombinant Ro protein produced pups with atrioventricular conduction abnormalities.^{8,15} Fourth, it would be important to demonstrate whether the presence of autoreactivity against cardiac tissues is associated with the development of cardiac arrhythmias in individual patients. This information is lacking.

Autoimmunity has received increased attention as a novel and important mechanism that underlies a host of cardiovascular disorders including cardiac arrhythmias. Autoimmune channelopathies portend arrhythmogenesis owing to alteration of electrical impulse generation and propagation. The association of an abnormal immune response with inflammation and oxidative stress suggests that cardiac substrate modulation may also be a major component of autoimmune-mediated arrhythmias. This whole area is currently underdeveloped and underappreciated. The precise autoimmune-mediated mechanisms of cardiac arrhythmias in patients with El Bagre-EPF are unknown, but deserve further investigation.

References

1. National Institute of Environmental and Health Sciences. Autoimmune Diseases Fact Sheet. Washington, DC: US Department of Health and Human Services; 11 2012.
2. Lerner A, Jeremias P, Matthias T. The world incidence and prevalence of autoimmune diseases is increasing. *Int J Celiac Dis* 2015;3:151–155.
3. Lee HC, Huang KT, Wang XL, Shen WK. Autoantibodies and cardiac arrhythmias. *Heart Rhythm* 2011;8:1788–1795. [PubMed: 21740882]
4. Emilsson L, Smith JG, West J, Melander O, Ludvigsson JF. Increased risk of atrial fibrillation in patients with coeliac disease: a nationwide cohort study. *Eur Heart J* 2011;32:2430–2437. [PubMed: 21653560]
5. Ahlehoff O, Gislason GH, Jorgensen CH, Lindhardsen J, Charlott M, Olesen JB, Abildstrom SZ, Skov L, Torp-Pedersen C, Hansen PR. Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish Nationwide Cohort Study. *Eur Heart J* 2012;33:2054–2064. [PubMed: 21840930]
6. Bacani AK, Crowson CS, Roger VL, Gabriel SE, Matteson EL. Increased incidence of atrial fibrillation in patients with rheumatoid arthritis. *Biomed Res Int* 2015;2015:809514. [PubMed: 25815336]
7. Bornholz B, Roggenbuck D, Jahns R, Boege F. Diagnostic and therapeutic aspects of β 1-adrenergic receptor autoantibodies in human heart disease. *Autoimmun Rev* 2014;13:954–962. [PubMed: 25149394]
8. Lazzerini PE, Capecchi PL, Laghi-Pasini F, Boutjdir M. Autoimmune channelopathies as a novel mechanism in cardiac arrhythmias. *Nat Rev Cardiol* 2017;14:521–535. [PubMed: 28470179]
9. Abreu-Velez AM, Howard MS, Velazquez-Velez JE. Cardiac rhythm and pace making abnormalities in patients affected by endemic pemphigus in Colombia may be a result of deposition of autoantibodies, complement, fibrinogen, and other molecules. *Heart Rhythm* 2018;15:725–731. [PubMed: 29277685]
10. Abreu-Velez AM, Howard MS, Jiao Z, Gao W, Yi H, Grossniklaus HE, Duque-Ramirez M, Dudley SC, Jr. Cardiac autoantibodies from patients affected by a new variant of endemic pemphigus foliaceus in Colombia, South America. *J Clin Immunol* 2011;31:985–997. [PubMed: 21796504]
11. Calkins H. Arrhythmogenic right ventricular dysplasia/cardiomyopathy—three decades of progress. *Circ J* 2015;79:901–913. [PubMed: 25877738]
12. Hoorntje ET, Te Rijdt WP, James CA, Pilichou K, Basso C, Judge DP, Bezzina CR, van Tintelen JP. Arrhythmogenic cardiomyopathy: pathology, genetics, and concepts in pathogenesis. *Cardiovasc Res* 2017;113:1521–1531. [PubMed: 28957532]

13. Huang YH, Kuo CF, Chen YH, Yang YW. Incidence, mortality, and causes of death of patients with pemphigus in Taiwan: a nationwide population-based study. *J Invest Dermatol* 2012;132:92–97. [PubMed: 21850023]
14. Jahns R, Boivin V, Hein L, Triebel S, Angermann CE, Ertl G, Lohse MJ. Direct evidence for a β 1-adrenergic receptor-directed autoimmune attack as a cause of idiopathic dilated cardiomyopathy. *J Clin Invest* 2004;113:1419–1429. [PubMed: 15146239]
15. Karnabi E, Boutjdir M. Role of calcium channels in congenital heart block. *Scand J Immunol* 2010;72:226–234. [PubMed: 20696020]