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Short Communications

Tricyclic Antidepressants and the Brugada Syndrome: An Example of Brugada Waves Appearing after the Administration of Desipramine

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Summary: Since its initial description in the early 1990s, the Brugada syndrome has become increasingly familiar to active researchers and practicing clinicians. The Brugada wave, a characteristic electrocardiographic abnormality of downsloping ST-segment elevation in leads V_1–V_3 and right bundle-branch block morphology, has now been associated with an increased risk of sudden death. Currently, very little is known about the relationship between the Brugada syndrome and tricyclic antidepressants. Accordingly, we report the case of a patient who developed prominent Brugada waves with the administration of increasing doses of desipramine. We believe the mechanism of Brugada wave augmentation or production secondary to tricyclic antidepressants is consistent with the current model of early repolarization. We also speculate that the increased risk of sudden death that may occur with tricyclic antidepressants could be related to the development of the Brugada syndrome. We advocate the judicious use of tricyclic antidepressants in cardiac and elderly patients, with careful monitoring of the electrocardiogram for the development Brugada waves.

Key words: Brugada, electrocardiogram, antidepressant, desipramine, tricyclic, sudden death, arrhythmia

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Introduction

Since its initial description in the early 1990s, the Brugada syndrome has become increasingly familiar to active researchers and practicing clinicians. The Brugada wave, a characteristic electrocardiographic (ECG) abnormality of downsloping ST-segment elevation in leads V_1–V_3 and right bundle-branch block morphology, has now been associated with an increased risk of sudden death, particularly in the Asian population.[1] Currently, very little is known about the relationship between the Brugada syndrome and tricyclic antidepressants (TCAs). Accordingly, we report the case of a patient who developed prominent Brugada waves with the administration of increasing doses of desipramine. The subsequent discussion utilizes the current understanding of this syndrome to explain the clinical significance of our findings.

Patient Presentation

History

The patient was a 77-year-old Caucasian woman who was brought to Emory University Hospital on April 9, 2001. She had a long history of bipolar disorder that had continued to worsen despite escalating doses of desipramine and lithium. Her psychiatrist hoped her symptoms would improve with electroconvulsive therapy (ECT) and sent her to the hospital for preprocedure evaluation. The ECG obtained on April 9, 2001 (Fig. 1) was significantly different from her baseline ECG recorded on March 12, 2001 (Fig. 2). The cardiology service was consulted regarding the abnormalities noted on the tracing.

The patient denied any recent cardiac problems. She had one episode of atrial fibrillation the year before that had been successfully treated by cardioversion. Other than a sister who died unexpectedly at age 77, the patient had no family history of arrhythmia, syncope, or sudden death.

Her medications included enalapril, atenolol, furosemide, warfarin, levothyroxine, rosiglitazone, metformin, lithium, and desipramine. The lithium and desipramine doses had been

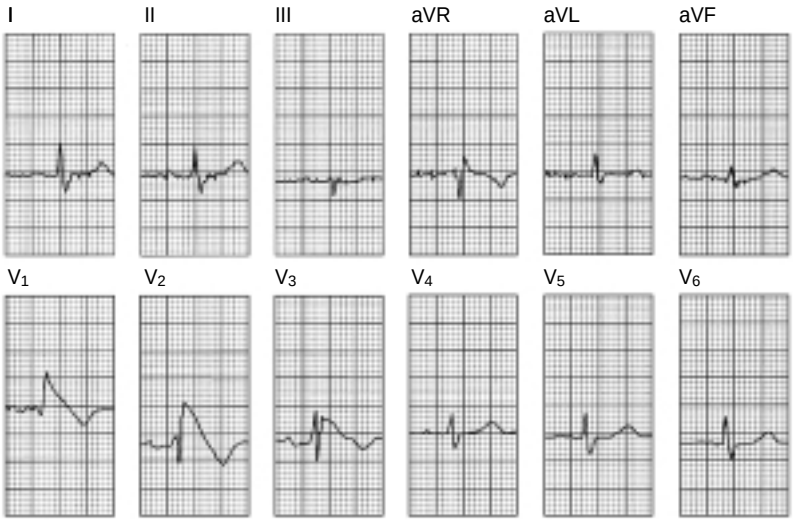

FIG. 1 April 9, 2001. Normal sinus rhythm is present at a rate of 60 complexes/min. The P-R interval is 0.20 s and the Q-T interval is 0.40 s. The duration of the QRS complex is 0.11 s. The terminal forces of the QRS complex are directed toward the right and anteriorly, indicating right ventricular conduction delay. The T waves are inverted in leads V_1–V_3, consistent with a mean T vector that is plus 40° in the frontal plane and 35–40° posterior. Brugada waves are noted in leads V_1–V_3. A vector representing the mean ST segment is directed anteriorly toward the right ventricle. Note that the initial portion of the ST segment is displaced to its maximum height at its onset, falling precipitously to blend with the inverted T waves. This pattern differs from the ST-segment abnormality produced by epicardial injury of anteroseptal myocardial infarction, in which an injury current creates its greatest amplitude during the middle of the ST segment.

increased to 450 and 100 mg daily, respectively, on March 14, 2001, 2 days after the ECG shown in Figure 2.

Physical Examination

The patient's heart rate was 60 beats/min, and her systolic and diastolic blood pressures were 115 and 51 mmHg, respectively. Auscultation of the heart revealed regular rhythm with no murmurs or gallop sounds. The second heart sound split physiologically, although right bundle-branch morphology was present on the ECG. There was no evidence of cardiac enlargement by palpation and no abnormality of the jugular veins. Peripheral arterial pulses were intact without bruits.

Laboratory Findings and Other Tests

Routine blood chemistries and cell counts were within normal limits. The ECG made on April 9, 2001 (Fig. 1) revealed right bundle-branch morphology with a QRS duration of 0.11 s and downsloping ST-segment elevation with inverted T waves

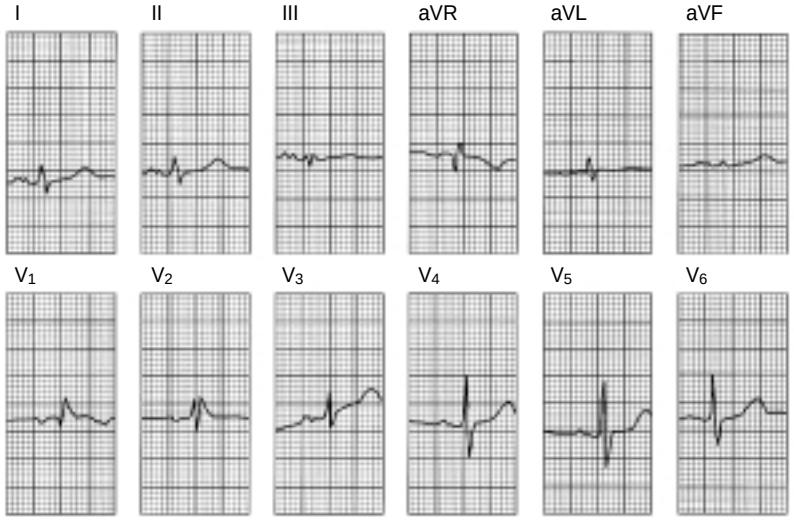

FIG. 2 March 12, 2001. Right ventricular conduction delay. Compared with Figure 3, the complexes in V_1 and V_2 may represent early signs of Brugada waves.

in leads V_1–V_3. An echocardiogram showed mild left atrial enlargement, minimal regurgitation of the tricuspid and mitral valves, and preserved ejection fraction.

Clinical Course

The members of the cardiology service felt that the ECG abnormalities were consistent with Brugada waves. Because these waves had become more prominent with the concomitant increase in desipramine dosage, discontinuation of the tricyclic antidepressant was recommended. The patient underwent ECT with minimal improvement in symptoms. She was discharged on divalproex sodium for mood stabilization. Lithium and desipramine were discontinued, and other preprocedure medications were resumed. Two months later, follow-up ECG (Fig. 3) made on June 6, 2001 showed persistent right ventricular conduction delay without Brugada waves.

Discussion

Over the past several years, researchers have attempted to gain insight into the mechanism of the Brugada syndrome by understanding the ECG finding of ST-segment elevation. The current understanding of the ST-segment abnormality is based upon what has been learned from normal human physiology as well as animal studies. Normally, during phase 2 of the ventricular action potential, the myocardium is homogeneous in voltage. The absence of a significant electrical gradient during this time is the reason that the ST segment is isoelectric in humans.[2] In animals, however, the ST segment may not be isoelectric. The voltage throughout phase 2 depolarization does not remain homogeneous because areas of the myocardium undergo early repolarization. Specifically, early repolarization occurs in the epicardium of the right ventricle, where transient outward channels (potassium) overwhelm the inward flux of calcium and sodium. In some human pedigrees, abnormalities of the sodium channel gene SCN5A have been linked to the autosomal dominant form of the Brugada syndrome.[3] It has been seen from animal studies that abnormalities of the outward potassium channel may also cause the ECG findings seen in this disorder.[4] Unfortunately, the pathophysiologic mechanisms may be more complicated than previously suspected because investigators are beginning to recognize three different morphologies of ST-segment elevation: straight (triangular shape), convex (coved), and concave (saddle-back).[5] The significance of the differing shapes remains unknown.

Of interest is the variability in the prominence of the ECG abnormalities. There appears to be a day-to-day variability seen in patients who are followed.[6] Changes in the autonomic nervous system also seem to have an effect. Beta-adrenoreceptor stimulation (isoproterenol) and alpha-adrenoceptor blockade (methoxamine, prazosin) reduce ST-segment elevation by increasing the inward calcium currents. Muscarinic stimulation (acetycholine provocation test, intravenous edrophonium, neostigmine), alpha-receptor stimulation (norepinephrine), and beta blockade (propanolol) all theoretically reduce the balance of inward calcium currents to outward potassium currents and consequently increase the amount of ST-segment elevation. Finally, class IA antiarrhythmic agents (procainamide, disopyramide) augment the ST elevation by blocking sodium channels and shortening the action potential in epicardial cells.[3] The importance of the changing ST segment is realized by the association of increasing ST elevation with the occurrence of ventricular fibrillation.[7,8]

The proposed mechanism for the ventricular arrhythmias is reentry. The heterogeneous repolarization abnormality creates significant differences in the electrical environment of the epicardium. These differences are the electrical substrate in which ventricular reentry circuits can occur. In animal studies, suppression of the reentry circuits by administration of outward ion channel blockers has been reported.[9]

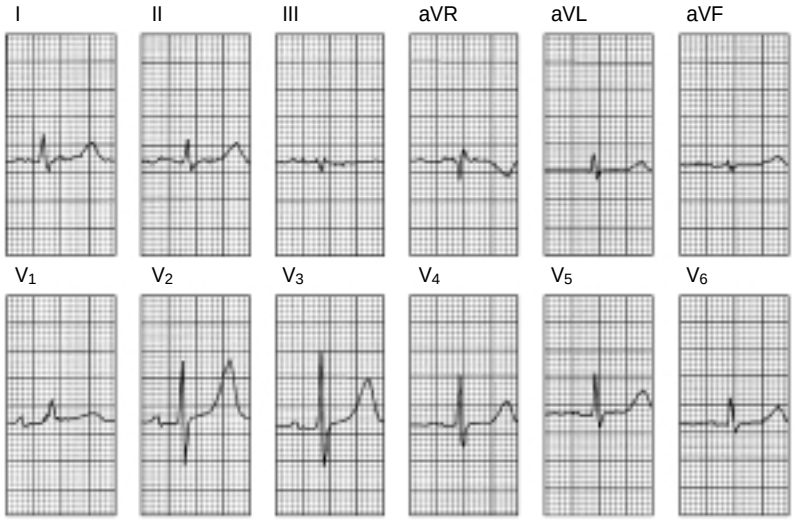

FIG. 3 June 6, 2001. This tracing shows right ventricular conduction delay, but no Brugada waves are seen.

It would follow logically that administration of tricyclic antidepressants, which possess class IA antiarrhythmic-like properties, could increase the ST-segment elevation in patients with Brugada waves and place this group at higher risk for sudden death. It is well known that TCAs can affect the heart at therapeutic levels, particularly in the elderly and in patients with underlying cardiac disease.[10, 11] An increased risk of sudden death associated with the use of TCAs has also been documented.[12] To our knowledge, this is the first reported case of a patient in whom Brugada waves were augmented or precipitated by routine TCA administration. One previous case has been reported with TCA overdose.[13]

Conclusion

We believe the mechanism of Brugada wave augmentation or production secondary to tricyclic antidepressants is consistent with the current model of early repolarization. We also speculate that the increased risk of sudden death that may occur with TCAs could be related to the development of the Brugada syndrome. We advocate the judicious use of tricyclic antidepressants in cardiac and elderly patients, with careful monitoring of the ECG for the development of right bundle-branch block morphology and downsloping ST-segment elevation in leads V_1–V_3.

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