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Management of Atrial Tachycardia in the Newborn With Enterovirus Myocarditis

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ABSTRACT

Neonatal enterovirus myocarditis is a rare but serious infection that is often an underrecognized cause of cardiovascular collapse. Enterovirus myocarditis in patients with such collapse should be suspected when signs of congestive heart failure and tachyarrhythmia are present. The majority of reported electrical disturbances associated with enterovirus myocarditis are ventricular in origin, but the infection can present as atrial tachyarrhythmia. Atrial tachyarrhythmias associated with enterovirus myocarditis are difficult to manage because of their resistance to conventional antiarrhythmic therapy. We present 2 cases of neonates with atrial tachycardia associated with enterovirus myocarditis who responded to a combination of amiodarone and flecainide.

INTRODUCTION

Enteroviruses (EVs) are a commonly encountered family of infections, especially in infants and children. Two distinct classes of EV exist: polioviruses (types 1, 2, and 3) and nonpolioviruses (coxsackievirus, EV, echoviruses, and unclassified EVs).[1] Nonpolio EV infections cause an estimated 10-15 million symptomatic infections annually in the United States.[1] Neonates with nonpolio EV infections are at a high risk of developing a sepsis-like condition, including meningoencephalitis, myocarditis, and hepatitis.[2] In addition, infants younger than 10 days are unable to mount a significant immune response and are at a higher risk of a serious infection from these nonpolio EVs.[2]

Clinical manifestations of EV myocarditis in neonates may include signs of congestive heart failure and tachycardia. The mechanism of EV-induced damage to cardiac myocytes is unknown, but it has been suggested that the mechanism is through a direct viral-mediated cytotoxicity as well as damage from the body's own immune response.[3] Abnormalities most commonly seen on electrocardiogram (EKG) in patients with EV myocarditis include sinus tachycardia, ST-T wave abnormalities such as elevation and/or depression, T wave inversion, ventricular tachycardia, and Torsades de pointes.[4,5]

Although EV myocarditis is typically associated with ventricular arrhythmias, supraventricular arrhythmias may also occur.[6] It has been postulated that the inflammatory response to EV infection leads to an invasion of lymphocytes into the myocardium and triggers the arrhythmias by generating automatic foci within the atrium.[7] Case reports in the literature have described atrial arrhythmias associated with EV myocarditis, including unifocal as well as multifocal atrial ectopic tachycardia.[4,6,8] We present a series of 2 neonates with atrial ectopic tachycardia associated with EV myocarditis, one of which was multifocal, who both responded to combination therapy with amiodarone and flecainide.

CASE 1

A 7-day-old African-American male, born at 37-5/7 weeks' gestational age, presented with a 1-day history of decreased oral intake, fever (38.3°C), and tachyarrhythmia. At birth, his mother was seronegative with unknown herpes simplex virus status, but she experienced symptoms of fever, malaise, and headache 2 days before the patient's admission. At an outside hospital, a sepsis work-up was unremarkable; the patient was admitted and treated with antibiotics. Upon admission, he had tachycardia, with

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a heart rate of > 250 beats per minute (bpm). Adenosine failed to terminate the rhythm, so he was transferred to our hospital for advanced cardiovascular care.

Significant findings on the admission physical examination were tachypnea (36-40 breaths per minute) and tachycardia (> 220 bpm). Echocardiogram revealed normal neonatal cardiac anatomy, normal coronary vessels, and low-normal systolic function with diastolic dysfunction. Early in the disease course, a direct fluorescent antibody (DFA) test of respiratory secretions was positive for rhinovirus. Rhinovirus and EV both belong to the family *Picornaviridae* and may cross-react in a DFA test. Subsequently, a viral polymerase chain reaction (PCR) panel confirmed a positive result for EV.

The EKG revealed multiple distinct P wave morphologies, irregular P-P intervals, and an isoelectric baseline between P waves; we diagnosed multifocal atrial tachycardia (Figure 1). The patient was intubated, and an esmolol drip was initiated and titrated from 50 to 200 mcg/kg/min intravenously. This treatment slowed his tachycardia rate from 230 bpm to 195 bpm. The patient then received 3 boluses of amiodarone (5 mg/kg) and was started on an amiodarone drip (15 mg/kg/d). When these antiarrhythmics failed to control his arrhythmia, oral flecainide at 80 mg/m^2/d was added. On the next day, he converted to sinus rhythm (120-140 bpm) with first-degree heart block. Flecainide was subsequently discontinued after 4 doses because of widening QRS complex, a known complication of rising flecainide levels.[9] At the end of the patient's hospital stay, echocardiography revealed normal cardiac anatomy, normal ventricular systolic function, and trivial mitral regurgitation; his EKG showed a normal sinus rhythm. The patient was discharged home on amiodarone (15 mg/kg/d). Tachycardia has not recurred, and the patient was weaned from amiodarone at 1 year of age.

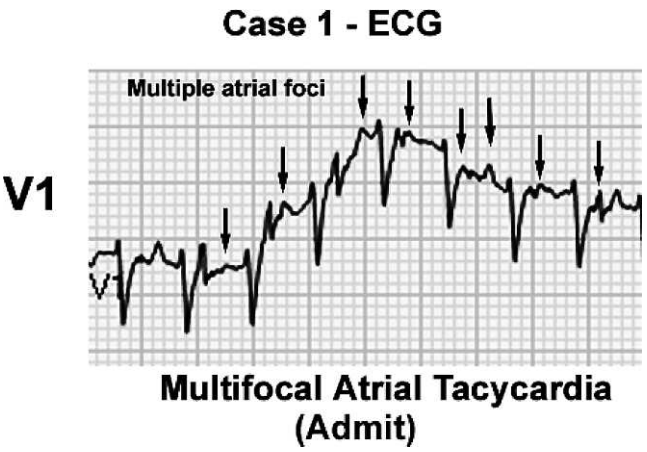

Figure 1. Electrocardiogram from case 1 demonstrating multifocal atrial tachycardia.

CASE 2

A 9-day-old Caucasian female, born at 35 weeks' gestational age, presented with irritability and tachyarrhythmia. Maternal history was negative for fever, cough, or runny nose, with no antenatal risk factors for EV infection. The patient originally presented to an outside hospital 2 days prior and was diagnosed with supraventricular tachycardia, which was successfully converted with adenosine. She was discharged home on propranolol and digoxin. Two days later, the patient became irritable, and her Holter monitor showed a tachycardia of 280 bpm. The patient was brought to our facility for further evaluation.

Significant findings on the admission physical examination included tachycardia (> 250 bpm), tachypnea (38-41 breaths per minute), and oxygen saturation of 94% on room air. A viral PCR panel was positive for EV infection. An EKG revealed a narrow-complex regular tachycardia at 280 bpm. Administration of a dose of adenosine (200 mcg) failed to convert the rhythm but caused a transient atrioventricular node blockade that revealed an ectopic atrial tachycardia with an atrial rate of 280 bpm. The patient received an amiodarone 5 mg/kg bolus, which rapidly converted her to normal sinus rhythm. She was then started on an intravenous amiodarone infusion (15 mg/kg/d) along with oral propranolol (4 mg/kg/d). She remained in sinus rhythm and was discharged on amiodarone and propranolol.

A week later, the patient was readmitted for recurrent tachycardia. She was given another amiodarone bolus (5 mg/kg) and started on amiodarone (15 mg/kg/d) and propranolol (4 mg/kg/d), which failed to adequately control her arrhythmia. Flecainide (80 mg/m^2/d orally) was then added to her treatment regimen. Initially, flecainide was reduced after an EKG revealed a right bundle branch block, a known side effect of flecainide toxicity.[10] She subsequently had several episodes of tachycardia (> 180 bpm), and both amiodarone and flecainide were titrated up to adequately control her rhythm. By the end of her hospital stay, she was not having any further episodes of tachycardia or right bundle branch block, and the patient was discharged home on amiodarone (15 mg/kg/d), propranolol (4 mg/kg/d), and flecainide (100 mg/m^2/d).

A few weeks later at a clinic visit, an EKG revealed a sinus rhythm with a partial right bundle branch block (Figure 2), indicating possible flecainide toxicity. Her flecainide level was 1.1 mcg/mL, which exceeded the

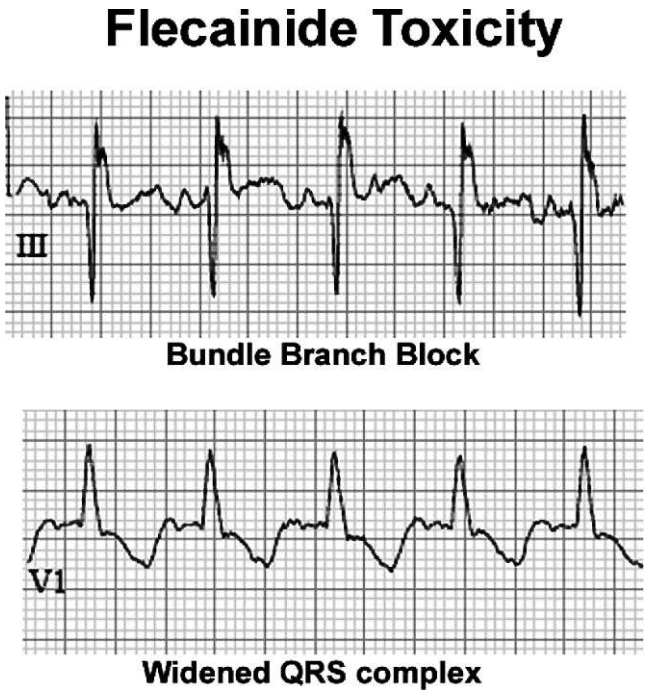

Figure 2. Electrocardiogram from case 2 demonstrating a wide QRS morphology consistent with flecainide toxicity.

therapeutic range (0.2-1.0 mcg/mL), and her flecainide dose was reduced to 80 mg/m^2/d. The tachycardia did not recur after a year's follow-up, so her medications were subsequently discontinued. She has been tachycardia free and off medications for the past year.

DISCUSSION

EV myocarditis may be an underrecognized cause of cardiovascular collapse in newborns. The diagnosis should be suspected when the following signs and symptoms are present: congestive heart failure, cardiomegaly, ischemic changes on the electrocardiogram, arrhythmia, and/or elevated cardiac enzymes. It can be difficult to discern which of these manifestations came first: Did the tachycardia cause the cardiomyopathy, or did the EV myocarditis result in both poor function and the tachycardia? In case 1, the patient presented with poor function in tachycardia with normalization of function after the tachycardia was controlled. This normalization of cardiac function could have been because of either the return to normal sinus rhythm or the spontaneous resolution of the myocarditis.

Management of atrial tachyarrhythmias associated with viral myocarditis is particularly challenging because of their resistance to conventional antiarrhythmic therapy. These cases demonstrate that therapy with amiodarone, digoxin, and beta blockers alone and in combination failed to adequately treat atrial tachyarrhythmia. Only when amiodarone and flecainide were used in combination did the tachyarrhythmias convert to normal sinus rhythm. This observation is in concordance with Fenrich et al,[11] who demonstrated that combined flecainide and amiodarone therapy was efficacious in refractory tachyarrhythmias in infants.

Amiodarone interacts with flecainide through the cytochrome P450 system that inhibits hepatic metabolism and causes a significant rise in flecainide plasma levels.[12] Therefore, flecainide should be started at lower doses, in the range of 40 to 80 mg/m^2/d, and signs of its toxicity must be strictly monitored. Flecainide toxicity generally manifests itself with EKG changes consistent with prolonged PR and widened QRS intervals.[9] In rare cases, a transient bundle branch blockade, as seen in our second case, may also present as a side effect to flecainide therapy.[10] Flecainide plasma levels are strongly correlated to the development of EKG changes.[9] Although direct monitoring of flecainide levels would be a useful method for monitoring the drug's toxicity, the lack of rapid flecainide testing in most hospitals makes this methodology impractical. Therefore, vigilance for the aforementioned EKG changes is the most practical method for monitoring flecainide toxicity.

CONCLUSIONS

Management of EV-induced atrial tachyarrhythmia is often challenging because it is frequently resistant to conventional antiarrhythmic therapy. In our case series, the combination of amiodarone and flecainide successfully converted our patients to normal sinus rhythm. Flecainide toxicity may occur, and close monitoring for EKG changes may facilitate early detection. Long-term outcomes of patients with myocarditis depend on the degree of recovery of ventricular systolic function but have been demonstrated to be favorable if the morbidities associated with initial presentation are successfully treated.

REFERENCES

1. Khetsuriani N, Lamonte-Fowlkes A, Oberst S, Pallansch MA; Centers for Disease Control and Prevention. Enterovirus surveillance—United States, 1970-2005. *MMWR Surveill Summ*. 2006 Sep 15;55(8):1-20.
2. Abzug MJ. Presentation, diagnosis, and management of enterovirus infections in neonates. *Paediatr Drugs*. 2004;6(1): 1-10.
3. Brunetti L, DeSantis ER. Treatment of viral myocarditis caused by coxsackievirus B. *Am J Health Syst Pharm*. 2008 Jan 15;65(2): 132-137.
4. Inwald D, Franklin O, Cubitt D, Peters M, Goldman A, Burch M. Enterovirus myocarditis as a cause of neonatal collapse. *Arch Dis Child Fetal Neonatal Ed*. 2004 Sep;89(5):F461-F462.

5. Badorff C, Zeiher AM, Hohnloser SH. Torsade de pointes tachycardia as a rare manifestation of acute enteroviral myocarditis. *Heart*. 2001 Nov;86(5):489-490.
6. Simpson KE, Hulse E, Carlson K. Atrial tachyarrhythmias in neonatal enterovirus myocarditis. *Pediatr Cardiol*. 2009 Aug; 30(6):827-830. Epub 2009 Mar 18.
7. Bradley DJ, Fischbach PS, Law IH, Serwer GA, Dick M 2nd. The clinical course of multifocal atrial tachycardia in infants and children. *J Am Coll Cardiol*. 2001 Aug;38(2):401-408.
8. Harris JP, Cecchin F, Perry JC. Infantile chaotic atrial tachycardia: association with viral infections. *Ann Noninvasiv Electrocard*. 2000 Jul;5(3):279-283.
9. Morganroth J, Horowitz LN. Flecainide: its proarrhythmic effect and expected changes on the surface electrocardiogram. *Am J Cardiol*. 1984 Feb 27;53(5):89B-94B.
10. van Aubel KJ, Ruiter JH, Arnold AE, Burgersdijk C. Pseudo infarction ECG pattern occurring during intravenous treatment with flecainide acetate. *Eur Heart J*. 1992 Jan;13(1):137-139.
11. Fenrich AL Jr, Perry JC, Friedman RA. Flecainide and amiodarone: combined therapy for refractory tachyarrhythmias in infancy. *J Am Coll Cardiol*. 1995 Apr;25(5):1195-1198.
12. Shea P, Lal R, Kim SS, Schechtman K, Ruffy R. Flecainide and amiodarone interaction. *J Am Coll Cardiol*. 1986 May;7(5): 1127-1130.

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