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Brugada Syndrome Manifesting Only During Fever in Patient with Septic Shock Secondary to Post-Obstructive Pneumonia

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Patient: Male, 63
Final Diagnosis: Multi organ failure/septic shock
Symptoms: Abdominal pain • bloating
Medication: —
Clinical Procedure: —
Specialty: Cardiology

Objective: Rare disease
Background: Brugada syndrome is a cardiac disorder associated with sudden death due to sodium channelopathy, most commonly the SCN5a mutation. There are 3 different patterns of electrocardiogram (ECG) changes characterized as type I, II, and III. ECG patterns consist of variations of incomplete RBBB and ST elevation in anterior precordial leads only. Treatment, if warranted, consists of implantable cardioverter-defibrillator.

Case Report: A 63-year-old male presented with abdominal pain for 4 days that was persistent, and after further imaging, he was found to have hepatic metastases from a stage IV small cell carcinoma of the lung. The patient was started on chemotherapy with carboplatin and VP-16. The patient decompensated, developed septic shock secondary to post-obstructive pneumonia, and eventually required intubation. He became tachycardic, and an ECG was ordered to evaluate the heart rhythm. It was determined that the patient had Brugada wave/syndrome. The patient's condition deteriorated with worsening septic shock, suspected type II NSTEMI, and multiorgan failure. The patient was designated DNR ("do not resuscitate") and passed away.

Conclusions: This case represents how channelopathies can be provoked with fever. It is believed that this occurs due to denaturing of the ion channel leading to abnormal ST segment changes typically seen on ECG and an increased risk of developing lethal arrhythmias. Spontaneous presentation of nondrug-induced Brugada syndrome carries an increased risk of deadly arrhythmia, for which this patient would have required electrophysiological studies. Unfortunately, this patient was unable to undergo genetic testing or electrophysiological studies, as he passed away.

MeSH Keywords: Brugada Syndrome • Fever • Shock, Septic

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Background

Brugada syndrome was initially described by the Brugada brothers in 1992. Normally the SCN5A gene encodes Nav1.5 cardiac sodium channel that is a component of the alpha subunit of the I_{Na} [1]. This SCN5A gene encodes a 216 amino acid sequence responsible for phase 0 cardiac conduction. This typically results in loss of function by decreasing sodium current [2]. Identified in 1998, this gene has greater than 100 kb which exhibit 28 exons. These channels are only found in the atrial and ventricular tissue. Over 100 pathologic variances have been identified. Other SCNA mutation diseases that are gain-of-function mutations rather than loss-of-function mutations cause long QT syndrome, progressive conduction system disease, atrial fibrillation, sick sinus syndrome type 1, dilated cardiomyopathy, and familial paroxysmal ventricular fibrillation type 1. Brugada syndrome is associated with other conduction abnormalities including 1st degree AV block, interventricular conduction delay, and sick sinus syndrome. There have been identifications of heterozygous and hemizygous pathologic variance. Approximately 75% of people are diagnosed by clinical history and ECG results alone. Brugada syndrome has been stratified into subtypes 1 through 16, which have been identified as representing greater than 350 genes that could potentially be involved [3].

There are 3 major morphology types of Brugada syndrome. Type 1 is considered diagnostic. Type 2 exhibits a saddleback appearance and type 3 can convey a coved or saddleback morphology; but neither carry diagnostic identification. J-point elevation greater than 2 mm with coved or downward convexity of the ST segment should be identified. ECGs demonstrate a right bundle branch block pattern with persistent ST segment elevations in the right precordial leads. Younger males with normal heart structure conveyed the highest incidence in sudden cardiac death likely secondary to ventricular fibrillation. This is thought to be responsible for approximately 12% of all sudden cardiac death cases and 20% of sudden cardiac death in patients without structural heart anomalies. The mean age of sudden cardiac death is 35 to 40 years old [3]. Symptoms may include syncope due to a persistent ventricular tachycardia and ventricular fibrillation. These symptoms typically are precipitated after large meals, resting, or while sleeping due to increased vagal tone. Also suspected is a hormonal influence which might influence the distribution of ion channels across the heart [4]. The global prevalence of Brugada syndrome is 5 to 20 per 10 000 [4]. Spontaneous abnormal ECGs represent an approximately 45% increased likelihood risk of caring an arrhythmic event [3]. The incidence of Brugada syndrome is 8–10 to 1, males to females [2]. This is an endemic situation in Southeast Asia. Brugada syndrome is the leading cause of sudden cardiac death in the young in this region [4,5].

Brugada syndrome is typically inherited in an autosomal dominant fashion, however, sporadic mutations comprise up to 60% of patients. There appears to be an incomplete penetrance which is frequent in females. Only 35% are determined to have a genetic etiology. The majority of these mutations encode subunits or trafficking/regulation of ion channel such as sodium, potassium, and calcium. Only 30% are identified as the best known SCN5A mutation, 5% have been identified as other, and 65% have no identification at all. Other physiologic derangement etiologies have been identified as DNA methylation disruptions, RNA errors, and problems with post-translation modifications [4]. Siblings are thought to have a 50% chance of inheritance. In actuality, developing type 1 Brugada syndrome is less than 50% secondary to incomplete penetrance. These genetic abnormalities can be identified with leukocyte DNA. If the parents of an affected patient are negative for Brugada syndrome then there is less than a 1% chance of a sibling inheriting Brugada syndrome. The offspring of a genetically confirmed mutated parent conveys a 50% chance of inheriting this syndrome [3]. Most individuals with a positive proband diagnosed have an affected parent with a proband. If the parents are positive, then they are encouraged to have an ECG with routine follow-up every 1 to 2 years. If the parents are negative, the inheritance may have been a *de novo* mutation or there is a germ line mosaicism yet to be identified [3].

The pathophysiology of Brugada syndrome has 2 leading postulates, the first being transmural dispersion of repolarization an ST segment elevation and the second being preferential conduction slowing in the right ventricular outflow tract resulting in the ST segment elevations in the right precordial leads. These regional differences in right ventricular epicardial conduction are aggravated by the decrease in inward sodium channels. This creates an epicardial reentrant excitation wave. This was demonstrated in 2009 by Boukens et al. as described by embryological development of the right ventricle and right ventricular outflow tracts [4]. Prolonged PQ, QRS, and H to V intervals are described. Sodium current dysfunction with local conduction blockades in the epicardium results in multiple spikes within the QRS complex that triggers a true ventricular fibrillation. This is more frequent with bradycardia due to increased vagal tone [3]. This creates a shift in gradient toward outward current I_o during phase 1 of the action potential and decreases the availability of sodium currents [3]. ECG patterns overlying the right ventricular outflow tract show slowing in depolarization/repolarization in spontaneous or provoked Brugada appearance by sodium channel blockers or by fever [5]. Drugs, testosterone (i.e. hormones), and fever have been identified as triggers. Compound mutations typically equate to more severe disease. Genetics are currently not useful in risk stratifications [4]. It is important to remember that 75% of people who are diagnosed by clinical history and ECG results do not have genetic testing, in the general population [3].

Provocative testing for Brugada syndrome is typically elicited by class 1A or 1C drugs including flecainide and ajmaline as the drugs of choice. Ajmaline challenges depend on noninvasive ECG imaging and whole heart conduction and repolarization patterns. It was found that the right ventricular outflow tract had the greatest influence and delay and recovery interval during these prolongations. The right ventricular outflow tract conduction delay correlated directly to the degree of J-ST point elevation. This correlation is proportional to the degree of conduction delay and not the prolongation in repolarization times [6]. When utilizing the oral flecainide challenge, one study looked at lead 2 in the prediction of a positive test with recognition of latent Brugada syndrome. QRS notching/depressed J-point conveyed a sensitivity of 87.5%, QRS lowering conveyed 100% sensitivity and lack of isoelectric ST segment, when all 3 are combined they had a high sensitivity in predicting inducible type 1 Brugada syndrome. When combining all of these together with the ST to QT ratio less than 0.24 and lack of isoelectric ST segment increased the specificity to 73.3% and a positive predictive value of 76% [7]. Individuals with SCN5A mutations only have a 20% to 30% chance of having a positive ECG. Approximately 80% have a drug-induced Brugada appearance on ECG with sodium channel blockade [3]. When the ECG demonstrates positivity, one must consider family history of sudden cardiac death in those less than 45 years of age, ECG-identified type 1 Brugada syndrome morphology relatives, or arrhythmia-related symptoms such as seizure, syncope, nocturnal agonal respirations, polymorphic ventricular tachycardia or ventricular fibrillation. AICD (automatic implantable cardiac defibrillator) implantation may be warranted as well as other prevention medications and interventions. Quinidine and phosphodiesterase inhibitors type 3 and radiofrequency ablation of ventricular ectopy over the right ventricular outflow tract of the anterior epicardium have all been described. If the patient is a symptomatic pregnant female, quinidine may be started after low-dose IV isoproterenol has been administered [3].

The prognostic significance of fever induced Brugada syndrome is relatively unknown. This is thought to be conveyed by F-type 1 subtype and is relatively asymptomatic. Spontaneous Brugada syndrome carries an increased risk for fatal arrhythmia. Drug-induced Brugada syndrome is thought to be relatively benign [8]. One study presented 112 patients who developed F-type 1 versus drug-induced ECG abnormalities. Of these 112 patients, 88 patients were evaluated for prognosis. The mean age was 45.8 ± 18.7 years; 71.6% were male and 21% conveyed having family history. Of these only 26.4% carried the SCN5A mutation. The risk of ventricular fibrillation was equal to 0.9% per year in asymptomatic patients. ST segment elevations during fever or drug challenges were not significantly different between the fever group and drug-induced group. Of notable mention, the PR interval was found to be decreased

in the fever group while the drug group conveyed an increase in PR interval and QRS duration. The F-type 1 group from this study did have an increased risk of arrhythmic events and was speculated to develop possibly through a more complex mechanism rather than drug-inducible form [8].

Other case reports have described febrile illnesses mistaken for acute myocardial infarction to where sepsis provoked Brugada syndrome that was misinterpreted as STEMI [9], a 29-year-old male with fever who met 7 out of 8 diagnostic criteria for hemophagocytic syndrome induced by *Chlamydomydia pneumoniae*; and a 76-year-old who underwent a syncopal event with witnessed ventricular fibrillation to where the ECG showed code type 1 Brugada pattern without a history of familial inheritance or sudden cardiac death in immediate family members [10]. Other cases have been described including a 48-year-old female who experienced dizziness and malaise after heat exhaustion that unmasked Brugada syndrome. There were depolarization/repolarization abnormalities by a temperature-dependent mechanism of wild type sodium channels and SCN5A mutated channels. This patient did not have a family history for sudden cardiac death. During this patient's evaluation after shifting electrodes and performing an ajmaline drug challenge, it revealed and provoked a type 1 Brugada pattern [11].

It is recommended that electrophysiology studies be performed, families are screened, and continued monitoring be performed on all patients with Brugada syndrome. Molecular genetic testing for family members is still controversial [3,4]. Implantable cardiac defibrillators are recommended for spontaneous cases for those that are symptomatic, and isoproterenol should be used for electrical storm. Prevention of Brugada syndrome with quinidine 1 to 2 g daily has been postulated. Surveillance should be continued every 1 to 2 years with ECGs for pathologic variants or in patients with high family history risk. These patients are told to avoid anything that might precipitate a fever if possible, antidepressants especially tricyclic antidepressants, vasotonic agents, beta-blockers, first-generation antihistamines, cocaine, alpha agonists, antipsychotics, certain anesthetics, and class 1A and 1C antiarrhythmics [3]. Sodium channel blockers amplify the existing I_{Na} and other ion channel defects. The potency of the drug is proportional to the rate of dissociation of the drug from the sodium channel [2]. Proband identification should be performed if they are having clinical symptoms with positive correlating ECGs [3].

Case Report

A 62-year-old male with a past medical history of chronic obstructive pulmonary disease (COPD), tobacco abuse with a 45 pack-year history of smoking, former alcoholism, and hypertension (HTN), presented to the hospital with feelings of

bloating and abdominal pain. He was sent to the Emergency Department (ED) after his primary care physician had performed some initial outpatient testing. The results showed elevated liver function tests including total bilirubin 2.0 mg/dL, alkaline phosphatase 394 IU/L, AST 112 U/L, and ALT 80 U/L. He stated his abdominal pain started 4 days ago and was epigastric in location. He had taken appropriate dosing of acetaminophen without any relief. His pain was rated a 10 out of 10 on pain scale without any radiation. There were no aggravating factors. The only associated symptom he noted was significant acute bilateral leg swelling. The patient denied any dyspnea, chest pain, urinary retention or frequency, headache, fever, or night sweats. In the ED the patient was found to have a leukocytosis of 16 900 WBC/mL with 84% neutrophil predominance, normocytic anemia with hemoglobin of 12.3g/dL, lipase >4000 U/L, lactate 1.7 mmol/L, CRP 25.3 mg/dL, troponin <0.012 ng/mL, PTT 27.9 sec, PT 15.1 sec, INR 1.31, and a clear urinalysis. Chest x-ray report revealed a mass like density in the suprahilar region of the left upper lobe with suspected postobstructive changes, consistent with neoplastic process. Computed tomography (CT) abdomen and pelvis with intravenous (IV) contrast showed hepatomegaly with diffuse, innumerable hypoattenuating nodules, nodular enlargement of the adrenal glands, and periportal, peripancreatic and mild retroperitoneal lymphadenopathy. He also had bilateral lower extremity venous duplex scans revealing no evidence of deep vein thrombosis. Right upper quadrant ultrasound revealed no evidence of enlarged common bile duct, only abnormal liver parenchyma and cholelithiasis.

The following day the patient was seen by an oncologist and underwent biopsy of the liver masses, CT chest with IV contrast, and magnetic resonance imaging (MRI) (with and without contrast) of the brain. CT chest revealed emphysema and a bulky left upper lobe tumor (8×10×11 cm), which obstructed the upper lobe bronchus, encased the main pulmonary artery and mainstem bronchus, with associated extensive mediastinal and supraclavicular lymphadenopathy and chest wall invasion. MRI of the brain revealed multiple metastatic lesions as well. Radiation oncologist was consulted for palliative radiation and the patient continued piperacillin/tazobactam for his pneumonia.

Two days later, the patient underwent palliative radiation to the brain. Subsequently, the pathology report from the liver biopsy revealed small cell lung cancer. The patient decided he wanted to go for port placement and begin chemotherapy treatment. He was started on carboplatin and etoposide and was also started on IV furosemide in an attempt to keep some of his lower extremity edema down for comfort. After furosemide had been started, the patient subsequently developed acute kidney injury. It had to be stopped and gentle hydration was started.

The patient started to develop a worsening leukocytosis and infectious disease was consulted for post-obstructive pneumonia and further recommendations. That same day, the patient became more lethargic, hypotensive, and developed hypoxic respiratory failure. Arterial blood gas revealed hypoxia of pO₂ 65 on 4 L nasal cannula, whereas the patient required no oxygen the day before. He was transferred to the intensive care unit (ICU) for close management.

While in the ICU, anterior posterior view chest x-ray was a poor inspiration film and possible mild congestion was found. It was felt the patient was developing septic shock as he became tachycardic into 120 s and systolic blood pressure dropped into low 80 s. He was started on low dose Levophed to maintain appropriate perfusion, and was given colloid instead of crystalloid in an attempt to improve blood pressure and hydration without causing worsening pulmonary edema. His antibiotic regimen was switched to levofloxacin and meropenem per infectious disease recommendation.

The following day, the patient's renal failure worsened, and he was unable to clear his airway of secretions. He agreed to be intubated for weakness and worsening respiratory failure. He was requiring high doses of norepinephrine to maintain a mean arterial pressure above 65 mm Hg, so he was started on vasopressin to help lower the dose of norepinephrine. The patient underwent bronchoscopy and sputum culture revealed *Enterobacter aerogenes* resistant to only cephalosporins. Blood cultures remained negative for greater than 48 hours.

He then started to develop intermittent sinus tachycardia and what appeared to be supraventricular tachycardia on telemetry. With the significant increase in vasopressor requirement and new heart rhythm, there was some thought for possible cardiogenic shock overlap, so an echocardiogram, troponins, and an ECG were ordered. Troponin resulted first at 1.36 ng/mL and climbed to 2.48 ng/mL. The patient was found to have a fever at that time of 40.3°C (104.6°F) and an ECG was obtained (Figure 1) that revealed type I Brugada wave indicative of Brugada syndrome. He was started on heparin drip with antiplatelet therapy for type II NSTEMI, but no beta blocker secondary to septic shock. Echocardiogram revealed a hyperdynamic left ventricle, right heart chamber dilatation, and elevated right ventricular systolic pressure.

This patient's vasopressor requirement slowly improved the following day. The patient underwent defervescence and his sinus tachycardia resolved. Repeat ECG performed revealed resolution of the Brugada wave seen earlier (Figure 2). He was able to be taken off of sedation and follow commands well and was extubated to bilevel positive airway pressure. Nephrology evaluated him for dialysis as he progressively became anuric. He agreed to begin dialysis and underwent dialysis for 2 days. The

Figure 1. This is the ECG obtained when the patient was febrile and tachycardic. The elevated J point, seen in the septal leads only and designated by the arrows, is characteristic of Brugada wave. Full interpretation of the ECG was as follows: rate was 132; rhythm was sinus; axis was ~60; PR was normal; QRS was Brugada in septal leads, type 1; ST, elevation in V1-V3; QRS Brugada without LBBB or RBBB or incomplete block; hypertrophy was none; P wave was no atrial enlargement; QRS wave was narrow; T wave was blunted but no deflection; U wave was absent; J point was maximum at 4 mm. Type 1 Brugada syndrome, QTc was 445.

patient became increasingly lethargic/prostrated and elected to pursue comfort care. All life saving measures was ceased. The patient passed shortly after.

Discussion

This particular case was interesting as it was a case of fever-induced Brugada syndrome (FIBS) in an older patient, as the mean age for Brugada syndrome is around 46 years old. Another interesting aspect of this case was that the patient also had small cell carcinoma, which could be a point of interest to see if further cases are associated with underlying malignancy. His PR interval was 158 ms, different than that which is normally seen, and which is a shortened interval with FIBS. It is unfortunate that we were unable to follow-up with this patient, as the risk for FIBS inducing arrhythmias is still unclear. Standard of care for all patients is to undergo electrophysiological studies. The patient only had a brother who was still alive. Current guidelines state that if a patient undergoes genetic testing and is found to have a known Brugada inducing mutation, then his family members should undergo testing as well. Patients with type I morphology or those with high-risk family history should have follow-up with routine ECGs. He

Figure 2. This is the ECG obtained after the patient's fever had resolved. As you can see, the Brugada wave is no longer present. Complete interpretation is as follows: rate was 99; rhythm was sinus; axis was ~60 degrees; QRS was incomplete RBBB; PR was normal; QRS was not prolonged; hypertrophy was none; P wave was left atrial enlargement; QRS wave was no elongation; T wave was no abnormality; U wave was not present; J point was not elevated.

would not have received a defibrillator as he was asymptomatic at this point, and he did not have a known family history of sudden cardiac death before the age of 45 years. However, he did not know much about his family; and this could pose a problem with this type of patient scenario. Pharmacologic management mainly consists of quinidine, which can also be a good alternative for those who refuse or have contraindications to defibrillator.

Conclusions

This case demonstrated one of many different causes of Brugada syndrome. Brugada is being recognized more often now, and early identification can play a major role in mortality benefit. Channelopathies being induced by fever are still an uncommon phenomenon, and each case can provide more information regarding treatment. Unfortunately, our patient was unable to undergo genetic testing to evaluate for underlying genetic defects. The mainstay of therapy for Brugada syndrome, if appropriate, would be aimed toward preventing lethal arrhythmias/sudden death and being able to defibrillate if a lethal arrhythmia occurs.

Conflicts of interest

None.

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