Phenotype Variant Brugada Pattern: An Early Sign of Propofol Infusion Syndrome

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ABSTRACT

This report demonstrates the first case of inferior phenotype variant Brugada Pattern (BP) as the presenting sign of Propofol Infusion Syndrome (PRIS). A 65-year-old male in respiratory failure receiving four consecutive days of high dose propofol developed ST elevations, hyperkalemia, and lactatemia. ST elevations noted were sharply down-sloping presenting in inferior leads.[1] Hyperkalemia was treated and propofol discontinued. This therapy resulted in improvement in EKG and favorable outcome. This case supports three conclusions: the existence of inferior variant BP, BP may be a strong initial sign of PRIS, and early recognition and action stopping propofol leads to favorable outcome in PRIS.[1-4]

INTRODUCTION

Propofol Infusion Syndrome (PRIS), once thought only to occur in children, has gained popularity in recent years due to its high morbidity and mortality in adults as well. Due to heightened awareness and detection bias, the incidence of PRIS is increasing. The cause of PRIS, hypothesized to be either by direct mitochondrial chain inhibition or dysfunctional fatty acid metabolism, remains unclear.[3] Since the infancy of the syndrome, cardiac conduction abnormalities and refractory bradycardia hhave been its hallmarks. Case reports have in fact linked PRIS to the sodium channelopathy Brugada Syndrome (BS) known to cause malignant dysrhythmias and sudden death.[2,4] ST elevation in a sharp down-sloping so called Brugada like pattern may be a strong initial sign of PRIS.[3] Many different presentations of PRIS have been described in the literature but the most consistent known finding is the use of high dose propofol infusion for long duration.[5] This risk factor often occurs in critically ill patients requiring propofol therapy for increased intracranial pressure.[2,5] Other known findings include metabolic acidosis, lactemia, Acute Renal Failure (ARF), hyperkalemia, elevated triglycerides (TAG), and rhabdomyolysis.[5] Early detection and cessation of propofol is the only known method to improve outcome in PRIS.[6] Therefore, discovering methods for early detection is imperative.

CASE FINDINGS

A 65-year-old Caucasian male presented to the Surgical ICU intubated for respiratory failure preoperatively for open lung biopsy. A CT scan from an outside hospital demonstrated pan-bronchiolitis and apical cavitation suspicious for Tuberculosis (TB). Arriving with significant bronchospasm, the patient required around the clock bronchodilators and deep propofol sedation up to institutional maximum dose of 80 mcg/kg/min. Steroids were held at that time until TB and other infectious causes ruled out. Pulmonary consultation recommended bronchoscopy, an additional Acid-Fast Bacilli smear (AFB) to complete the work up for TB, and viral cultures. On the next hospital day, propofol wean was attempted unsuccessfully. Subsequently, on hospital day three, ketamine and muscle paralysis were added to reduce propofol requirements. Propofol 80 mcg/kg/min was still required to maintain oxygen saturations of 89% while permissive hypercapnia continued. Since bronchospasm continued and TB ruled out, intravenous steroids were initiated.

On hospital day four, after several days of maximum dose propofol, the ICU nurse noted changes in the telemetry strip that were concerning. The bizarre telemetry strip led to the 12 lead EKG seen in Figure 1A. Labs were drawn and the patient was found to be in ARF with acidosis (PH=7.21) and hyperkalemia of 6.5. The hyperkalemia protocol was initiated which included calcium gluconate, D50/insulin combination, albuterol, and kayexalate. Sodium bicarbonate was withheld for concern of worsening acidosis since ventilation was suboptimal. The arterial blood gas (ABG) at that time showed that the once compensated hypercapnic respiratory failure now was decompensated with new onset metabolic derangement and an elevated lactate of 2.2. Lasix was given in favor of hemodialysis since urine output was adequate. Cardiac enzymes were negative for MI, and thus EKG changes were attributed to ARF. Since the patient's condition had not improved, another set of cardiac enzymes were done and a chest wall echocardiogram was performed. Negative enzymes and an echocardiogram that showed no regional wall or structural abnormalities, ruled out myocardial infarction. Hyperkalemia, acidemia, and elevated lactate however persisted. The repeat EKGs seen in Figures 1B-1D were becoming more bizarre and paroxysmal atrial fibrillation was reported.

PRIS was discussed and propofol was discontinued in spite of normal creatinine phosphokinase (CPK) and (TAG) at that time. Aggressive diuresis with Lasix and Diuril in favor of hemodialysis was continued since urine output remained robust. Six hours after repeat diuretics were given and propofol discontinued, the hyperkalemia and acidosis improved. The 12-lead EKG returned to baseline morphology as seen in Figure 1E. Since the patient made dramatic improvement, he was transferred to Medical ICU for further pulmonary treatments. EKG

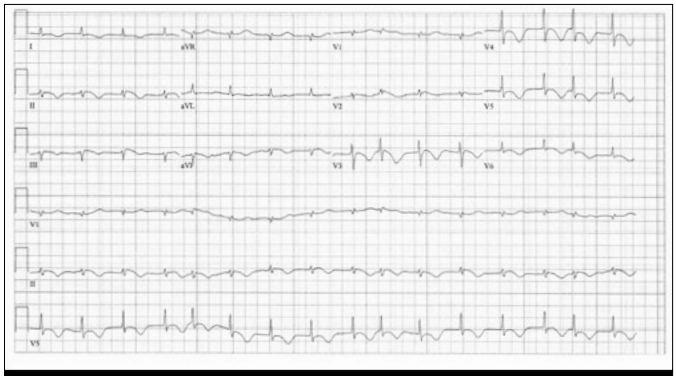

Figure 1A.

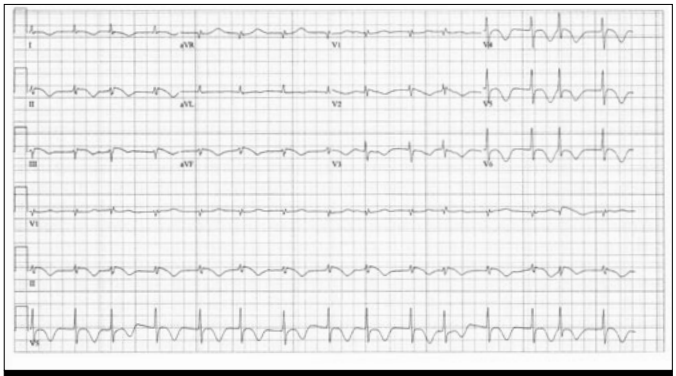

Figure 1B.

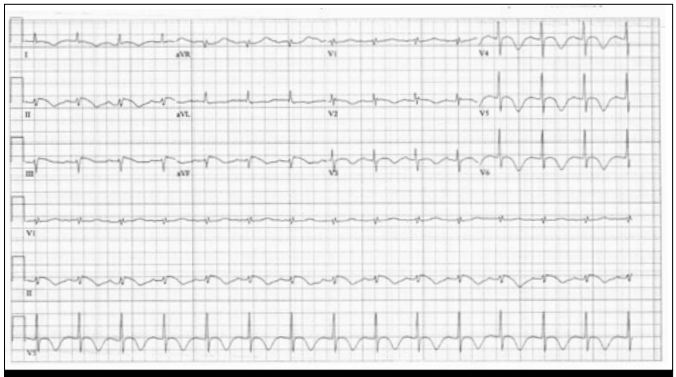

Figure 1C.

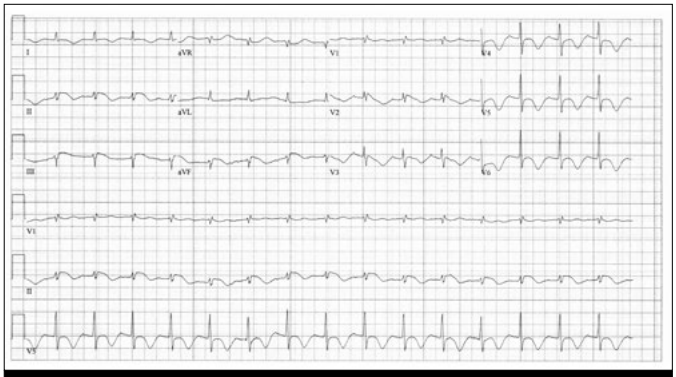

Figure 1D.

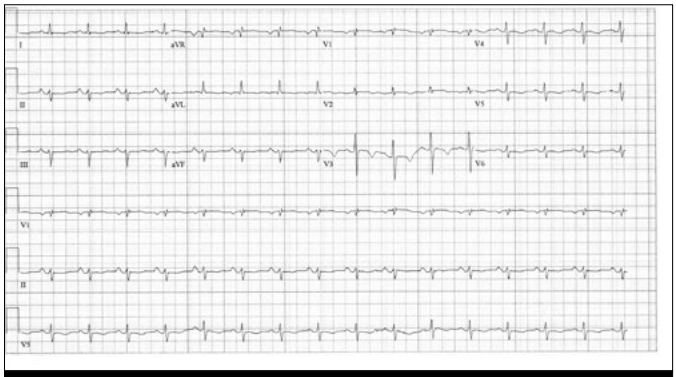

Figure 1E.

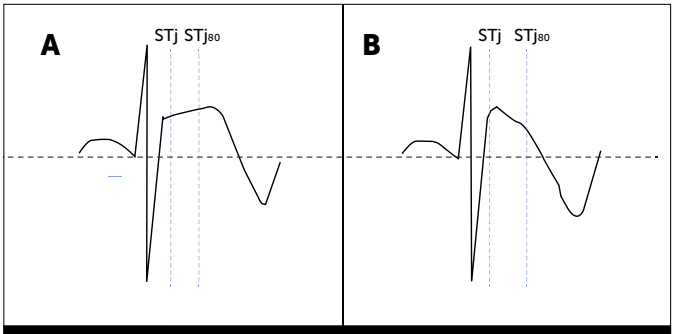

Figure 2.
Comparison between ST elevation in Early Repolarization (A) with Brugada Syndrome (B)

evolution was sent to the electrophysiology department for further analysis so that follow up with the patient could be maintained.

DISCUSSION

ST elevation (STE) is common in the ICU and includes an extensive differential. STE is considered to reflect acute transmural ischemia caused by an occlusion of a coronary artery by a thrombus until proven otherwise.[7] As per the 2013 ACCF/AHA Management Guidelines, STEMI is a clinical syndrome that comprises of typical symptoms of acute ischemia of the heart muscle in conjunction with elevation of the ST segment and increased blood levels of biomarkers that indicate necrosis of the cardiac muscle.[8] Therefore, it is recommended that patients with suspected acute STEMI receive immediate revascularization therapy to the occluded artery by either percutaneous coronary intervention or fibrinolysis. The decision to proceed with angiography or give thrombolytic

is made based on symptoms and STE analysis, and is usually reached before biomarkers such as troponins are detectable in the blood.[7] Symptoms however often present atypically; or as in this case, a patient may be sedated and intubated precluding the ability to elicit the classic ischemia symptoms. A detailed list of non-ischemic causes of ST elevation can be found in Table 1.[9]

Table 1. List of non-ischemic causes for ST elevation

1	ST elevation secondary to LVH
2	ST elevation secondary to conduction defect (such as left bundle branch blockage and non-specific intracardiac conduction delay)
3	Early repolarization pattern (notched J-point typically in anterollateral leads
4	Hypercalcemia Normal variant of ST elevation (ST elevation mostly ˆnleads V2-V3)
5	Concave ST elevation
6	Spontaneously reperfused STEMI
7	Aneurysm/old myocardia infarcation
8	Pericarditis/myocarditis
9	Wolf-Parkinson-White syndrome (pre-excitation)
10	Brudgada pattern
11	Takotsubo (apical ballooning) syndrome
12	Takotsubo (apical ballooning) syndrome
13	Hyperkalemia
14	Hypercalcemia

After reviewing the serial electrocardiograms, the negative chest wall echocardiogram and biomarkers, the most plausible explanation of the STE consisted of either Brugada pattern or hyperkalemia. In patients with acutely elevated serum potassium levels, pseudomyocardial infarction pattern has been reported to appear as massive STEMI that develops secondary to derangement in myocyte repolarization.[10] The existence of a "Brugada Phenocopy" has been described to exist secondary to various reversible causes such as electrolyte abnormalities.[4,11] However, this seems unlikely given that the potassium never exceeded 6.5 and the typical pattern of peaked T waves, widening QRS, PR interval prolongation never appeared. A prolonged QT interval up to 610 milliseconds was noteworthy, but again this is not specific for hyperkalemia, and in fact is found more in toxic drug related malignant arrhythmias such as PRIS. Moreover, EKG changes persisted inspite of correcting the hyperkalemia which contradicts a sole diagnosis of hyperkalemia to explain the STE.

Type 1 Brugada pattern typically presents as STE with at least 2 mm down-sloping "coved-type" in the anterior precordial leads (V1-V3) followed by deep wide T wave inversions.[1,2,11,12] This pattern can occur spontaneously or after provocation with a sodium channel blocker[12]. The Brugada syndrome is linked to an increased risk of ventricular arrhythmia and sudden cardiac death.[1,2,12] Figure 1 compares the classic morphology in BS contrasted with the benign Early Repolarization (ER) phenomenon.[13] The Ratio of the J point (STJ) to the point 80 milliseconds after the J point (STJ80) is called STJ/STJ80. In BS, this ratio is characteristically greater than one. Less than one identifies an upward sloping ST segment as occurs in ER. An STJ/ST80 ratio <1 is a highly accurate parameter for differential diagnosis between ER and BS, with sensitivity of 97%, specificity of 100%, and diagnostic accuracy of 98.7%. In addition, multivariate analysis showed that the STJ/ST80 ratio is superior to other electrocardiographic parameters previously reported, such as QRS duration and degree of STE.[13]

ence of ECG with a Brugada-like pattern in a patient with documented history of ventricular fibrillation or polymorphic ventricular tachycardia, or a history of sudden cardiac death in family members that are younger than 45 years, comparable ECG configuration in relatives, unexplained syncope, ability to induce ventricular tachycardia with programmed electrical stimulation, or agonal respiration at night.[12] The EKGs in Figures 1B-1D clearly demonstrate classic morphology of Brugada pattern in the anterior precordial leads (V2-V3) when the metabolic derangements and repolarization abnormalities peaked. However, the initial and most pronounced STE pattern can be seen in the inferior leads (II, III, AVF) lending this case more to the phenotype variant Brugada pattern.[1] Given that this patient lacked a history of sudden cardiac arrest, syncope, or malignant arrhythmia on telemetry, electrophysiological specialists at our institution labeled this phenomenon a "drug-induced Brugada-like ECG pattern" consistent with a toxic metabolic derangement.

PRIS, a channelopathy, which has not been fully elucidated, frequently presents inconsistently. Elevated TAG, ARF, hyperkalemia, rhabdomyolysis, and lactic acidosis are classic findings.[3-5,14] It is unclear how many signs must exist to make the diagnosis and which patients are susceptible. Consistently, PRIS case reports implicate long durations of high dose propofol.[5] Vernooy et al. described 67 patients with head injury that received prolonged propofol infusions, seven had been identified as having propofol infusion syndrome. Six of the seven PRIS patients developed the Brugada-like EKG and died within hours. The other 60 patients did not develop ventricular arrhythmias, suggesting that the mechanism underlying the arrhythmogenesis in PRIS is similar to that responsible for ventricular arrhythmias in the BS.[2] Frequently, case fatalities are diagnosed too late. Similarly, cases of

survival are documented when propofol is discontinued early and perhaps at times go unreported because of favorable outcome defending the importance of this case report.[6]

Moreover, PRIS has been linked to BS in previous reports but no gene study to date has definitively linked the two syndromes.[4] Twenty percent of BS is linked to a genetic defect of the Na+ channel. Propofol has significant neurologic and myocardial sodium channel inhibitory effects presenting the possible overlap in the two syndromes at the gene level.[4] The Brugada SNP could be analyzed in PRIS patients and may have a reasonably high frequency meriting investigation. I believe future research is essential because both syndromes are potentially deadly and under-investigated. Perhaps in the past PRIS has gone underdiagnosed in adults since it was originally thought to be a childhood syndrome. However, in the past decade, the diagnosis has been established in adults, thus, there is an increased incidence as a result of heightened awareness of the syndrome.

This diagnosis of PRIS could be debated. Although the classic diagnosis of PRIS presents with elevated CPK and TAG in the thousands, I argue that elevated CPK is a late finding of the syndrome. Elevated CPK signifies cell death and should be considered ominous in this condition. Moreover, while elevated TAG demonstrates altered fat metabolism, patients receiving propofol without the PRIS phenotype often demonstrate elevated TAG, green urine, and pancreatitis. Elevated TAG therefore does not necessarily imply toxic effects to the organs, rather it simply means over-usage of Propofol and should warn against continued high dose. Indeed several cases of normal CPK and TAG levels have been reported in patients with PRIS.[15]

In conclusion, early recognition of PRIS is crucial to preventing bad outcomes.[2,6] This can be accomplished by ordering daily triglyceride levels, blood gases looking for lactic acidosis, and doing routine daily 12-lead EKG in the setting of a patient on high dose propofol for increased duration. The goal should be to make fewer autopsy diagnoses of PRIS by discontinuing the propofol early.[6]

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