A Unique Instance of Wolf–Parkinson–White Pattern and Congenital Long QT Syndrome

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ABSTRACT. Case: We describe a unique instance of Wolf-Parkinson-White Pattern and Congenital Long QT Syndrome in the same patient. A 31 year old female with past medical history of pre-eclampsia during her last pregnancy and Wolf-Parkinson-White (WPW) pattern on EKG, presented to the hospital with complaints of palpitations and dizziness five days post-partum. Electrocardiogram (EKG) demonstrated a prolonged QTc and intermittent ventricular preexcitation pattern. Patient was found to have episodic pause dependent Torsades de Pointes (TdP) that were non-sustained but highly symptomatic. Given the patient’s presentation and persistently prolonged QT interval an implantable cardioverter defibrillator was implanted. Genetic testing and family counseling were performed. None of the typical known mutations that have been described with Long QT Syndrome(LQTS) were found in our patient. However, such testing may be unrevealing or “negative” in up to 20-25% of patients with LQTS and TdP

Conclusion: Wolf-Parkinson-White (WPW) pattern and congenital long-QT syndromes (LQTS) individually represent rare clinical entities. The concurrent clinical expression of both entities in a single patient is extraordinary. Our case report represents the unique instance of previously asymptomatic congenital LQTS in a patient with an intermittently pre-excited EKG.

KEYWORDS. Long QT syndrome, Torsade de pointes (TdP), Wolf–Parkinson–White.
Figure 1: a. Initial ECG on admission with prolonged QT-660, QTc523. b. ECG at the time of admission showing intermittent pre-excitation. c. ECG from 1 year ago showing fully pre-excited WPW.
procainamide (PCA) was administered (1,450 mg bolus followed by 1 mg/min constant infusion). The admitting physicians caring for the patient believed that the patient’s complaint of palpitations may have been secondary to PSVT, either orthodromic or less likely antidromic (given intermittent manifest pre-excitation pattern on ECG suggesting a long refractory period of the accessory pathway). Although the prolonged QT interval and bradycardia were noted, drug administration was believed to be appropriate by the admitting physicians in an effort to decrease accessory pathway conduction by pharmacologically prolonging the refractory period. Following procainamide administration, the QT interval markedly prolonged (Figure 2), and there was no further evidence of manifest pre-excitation. However, the patient was noted to have episodic pause-dependent torsade de pointes (TdP) that were non-sustained (Figure 3), but highly symptomatic (palpitations, presyncope). At that point in the patient’s course, an electrophysiology consultation was obtained and the patient was thereafter managed with the placement of a temporary pacing catheter at the right ventricular apex, pacing at a rate of 80 bpm so as to “overdrive” the arrhythmia and prevent further pause-dependent TdP. Procainamide therapy was immediately discontinued, potassium maintained at a level >4.0 mEq/l, and magnesium administered intravenously. Despite discontinuation of PCA, ventricular pacing, and medical interventions outlined above, the patient remained bradycardic in the absence of β-blocker therapy with heart rates <50 bpm (when not paced), but more importantly, marked QT prolongation persisted. Five days after discontinuation of PCA, the QTc averaged >500 ms (Figure 4). The patient’s age, gender, postpartum state, inability to administer β-blocker therapy, and a QTc>500 ms indicated a continued lifetime arrhythmia risk, especially since she wished to have future pregnancies. Accordingly, she was offered and agreed to receive a dual-chamber implantable cardioverter-defibrillator (ICD; Figure 5). Dual-chamber pacing (atrial based) allowed the use of maximal β-blocker therapy, which is indicated in the treatment of most patients with LQTS.

**Discussion**

Wolf–Parkinson–White (WPW) pattern and congenital long QT syndrome (LQTS) individually represent rare clinical entities. The prevalence of a WPW pattern on the surface ECG is estimated at 0.13–0.25%,1–3 while the incidence of LQTS is estimated to be 1/2500–1/10,000.4–6 The concurrent clinical expression of both entities in a single patient is extraordinary. Our case report represents the unique instance of previously asymptomatic congenital LQTS in a patient with an intermittently pre-excited ECG. Prior to our case, Breijo-Marquez et al.7 have described a similar individual. Additionally, a rare form of familial WPW syndrome has been documented with the etiologic mutation occurring in the PRKAG2 gene, which is responsible for the gamma-2 regulatory subunit of AMP-activated protein kinase.8 This protein kinase regulates the metabolic pathway of glucose metabolism. Phenotypically, this mutation acts in a way similar to the autosomal recessive Pompe’s disease, and therefore encodes a metabolic pathway resulting in a cardiomyopathy, i.e. structural, rather than an ion channelopathy. Whether other, yet to be discovered, mutations can link the structural disarray causing...
accessory pathway conduction and ion channelopathies resulting in potentially lethal arrhythmias remains to be elucidated.

However, the majority of patients with accessory pathway conduction, whether manifest or concealed, rarely manifest structural cardiac disease. When present, congenital heart disease is most often limited to right-sided abnormalities with Ebstein’s anomaly having the strongest association. Such individuals may demonstrate up to a 10% incidence of accessory pathway conduction with right free wall and posteroseptal tracts being most common. Other congenital abnormalities include congenitally corrected transposition of the great arteries, AV septal defects, and hypertrophic cardiomyopathy. Embryologic malformations disrupt the tricuspid and mitral valve rings, creating muscular tracts that cross the AV grooves, and thereby bypassing the AV node, resulting in manifest and/or concealed conduction. In those individuals with WPW and documented arrhythmia, approximately 4% will have a first-degree family member with pre-excitation, usually inherited as an autosomal dominant.

WPW syndrome is believed to be caused by accessory pathways that are composed of muscular tissue that results in electrical connections from atrium to ventricle and may conduct a wave of depolarization in either direction or both depending on the impedance on either side of the connecting tissue. The AMP-activated protein kinase when adrenergically stimulated may be responsible for the arrhythmias seen in such patients, as well as sudden cardiac arrest. Such mutations may potentially include enzymes that can affect ion channels and possibly cardiac repolarization potassium currents in phase 3 of the action potential which can result in malignant arrhythmias that are associated with QT prolongation. Atrial fibrillation and conduction defects have been observed in a familial syndrome that is involved in the regulation of ion channels. It may only be a matter of time and effort before a genetic association is established between WPW and LQTS.
As is well known, LQTS is a heterogeneous entity adversely impacting action potential duration and the process of myocardial repolarization. In addition, LQTS can be secondary to an inherited or random genetic mutation or may be an acquired condition. Either mutation etiology can lead to fatal arrhythmias, most notably secondary to TdP. It is believed that a reduction in net repolarization currents, usually due to a loss of function of an ion channel that conducts in the outward direction (rectifying current) is most often the cause of this syndrome. However, a gain of function resulting in inward currents may also cause the action potential duration to inappropriately prolong and increase the QT interval and risk of arrhythmia. Spatial dispersion of repolarization may therefore be the underlying causal factor in the emergence of early after depolarizations resulting in the appearance of “triggered” malignant arrhythmias.

At this point, genetic testing has been able to identify at least 12 different loci for the known types of congenital LQTS, but greater than 700 different mutations have been described. LQTS 1, 2, and 3 have the greatest prevalence. A QTc of >440 in males and >460 ms in females is generally accepted as prolonged and thus abnormal. However, the measurement of the QTc can vary in response to a number of factors. These include, but are not limited to, autonomic state, hormonal changes, electrolyte imbalance, drugs, penetrance of the mutation, and diurnal variation. Therefore a single ECG measurement may not be sufficient to diagnose QTc prolongation, congenital or acquired. Exercise testing and acute drug testing may also be required to make the correct diagnosis. A complete family history is essential. The primary goal in the management of patients with LQTS is to identify and mitigate, if not eliminate the risk of SCA. In our particular patient, peripartum hormonal changes may have played an important role in susceptibility to arrhythmia. Females in general have a higher risk for arrhythmia in LQTS, especially in the postpartum state. The presence of bradycardia may have led to an intensification of this risk as well.

Management strategies may include β-blockers, pacemakers, elimination of offending medications (which affect rapidly activating delayed rectifier potassium channels IKr), and the placement of an ICD. Lifestyle
changes requiring activity restrictions are often mandatory, but currently left cardiac sympathetic denervation is infrequently performed secondary to this procedure’s known complications.\textsuperscript{23} The life-time risk of malignant arrhythmia in this patient was felt to be high due to her prolonged QT at rest, and her demonstrated ability to generate TdP with drugs affecting repolarization (Ikr).\textsuperscript{24} Nonetheless, identifying the “high-risk patient” can be difficult at best. Given this patient’s desire to have future pregnancies, the presence of resting bradycardia, QT prolongation, and the unpredictability of drug exposure during her lifetime, along with the inability to administer β-blocker therapy due to bradycardia, the decision was made to offer the patient ICD therapy with pacing capability in this unusual and extraordinary circumstance. The ability to pace the atrium would allow the addition of pharmacologically relevant β-blockade. A subcutaneous ICD (S-ICD) was considered, but felt to be a suboptimal choice given the lack of atrial pacing capability.

In terms of this patient’s apparent channelopathy, genetic heterogeneity, and overlapping phenotypes as well as amino acid substitutions may have subtle or more manifest effects on the surface ECG.\textsuperscript{25,26} Genetic testing and family counseling were performed. None of the typical known mutations that have been described were found in our patient. However, such testing may be unrevealing or “negative” in up to 20–25% of patients with LQTS and TdP.\textsuperscript{27,30} Mutations in channel locales that have an impact on ion transfer and regulation can result in significant dysfunction in ion channel activity. mRNA splicing mutations have also been implicated.\textsuperscript{28}

Figure 5: Placement of a dual-chamber ICD.
Abnormalities such as those just described may account for the finding of negative genetic testing.

The ECG pattern in our patient was suggestive of LQTS 3, i.e. late-appearing T waves that were peaked and with a steep downslope, secondary to a “gain of function” SCN5A mutation. Of interest, this mutation has been associated with bradycardia, which was also demonstrated in this patient, in the absence of negative chronotropic agents. Nonetheless, testing did not uncover this particular mutation, or any of the commonly documented loci associated with this repolarization abnormality. However, as previously mentioned, genetic testing may be unrevealing in 25% of patients with established LQTS and arrhythmia. This patient also demonstrated a second electrical abnormality, WPW. Pre-excitation indicates the presence of an accessory atrioventricular conduction pathway. This may represent WPW pattern or syndrome. The latter represents an accessory pathway (myocardial tissue connection) resulting in episodes of arrhythmia. Such episodes may include PSVT (antidromic or orthodromic) and an increased risk of paroxysmal atrial fibrillation with rapid ventricular response and potential for associated sudden cardiac arrest. WPW pattern is by far more common than WPW syndrome. It is important to note that our patient was known to have WPW pattern, and had an ECG in the past that was fully pre-excited, but had no history of symptomatic or documented PSVT. The presence of intermittent WPW pattern on the 12-lead ECG suggested an accessory pathway with a long refractory period, making antidromic AV reciprocating tachycardia and paroxysmal atrial fibrillation with rapid ventricular response unlikely. The possibility of multiple accessory pathways, whether manifest or concealed, however, could not be excluded in the absence of comprehensive electrophysiologic study.

Such a study was not performed as it would not have altered the clinical decision-making process.

In summary, both congenital LQTS and evidence of pre-excitation is rare and may be responsible for potentially life-threatening situations. Careful evaluation is a necessity for correct diagnosis and expert consultation is required to appropriately manage these conditions. The use of antiarrhythmic agents and other medications that can adversely affect myocardial action potential duration and repolarization can complicate the management of patients with LQTS and therefore be used with caution, especially in the outpatient setting. It is likely that with time, a genetic connection may be established between the embryologic mutation resulting in accessory pathway formation and the concurrent appearance of repolarization abnormalities due to an ion channelopathy that can result in QT prolongation and TdP.

References

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