

Clinical Significance of Prolonged QTc Interval in Williams Syndrome

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Williams syndrome (WS) is a congenital developmental disorder affecting the connective tissue, neurologic, and cardiovascular (CV) systems in 1 in 8,000 live births.¹⁻³ The characteristic features of WS, including facial dysmorphisms, cognitive traits, and CV abnormalities, are known to arise from the deletion of approximately 28 genes on chromosome 7q11.23.³ Structural CV abnormalities occur most commonly and are present in approximately 80% of all patients with WS,⁴ and 93% of those presenting in the first year of life.⁵ The most common CV abnormalities in WS include arterial stenoses such as supra-aortic stenosis and peripheral pulmonary arterial stenosis,⁴ resulting from hemizygosity of the *ELN* gene, which encodes elastin.⁶ There is also a known increased risk for sudden cardiac death in this population that is 25-fold to 100-fold greater than in the general population.^{7,8} In a review of the published research, Burch et al⁹ surmised the sudden death risk to be essentially entirely the result of myocardial ischemia, especially in the setting of concomitant supra-aortic stenosis and stenosis of the coronary ostia. Kounis et al¹⁰ proposed that sudden cardiac death in WS may be related to an allergic coronary syndrome secondary to anesthetic exposure, and a recent report by Gupta et al¹¹ has given credence to that hypothesis.¹²

In an attempt to evaluate potential prolongation of the corrected QT (QTc) interval noted on electrocardiography in patients with WS, and to correlate electrocardiographic findings with sudden death, we recently published the experience at the Children's Hospital of Philadelphia in *The American Journal of Cardiology*.¹³ In that study, the prevalence of QTc prolongation in patients with WS was 13.6%, compared to a prevalence of 2% in healthy controls. Death occurred in 4 patients with WS, 2 of whom had evidence of QTc prolongation. An autopsy on 1 of the patients with QTc prolongation demonstrated no evidence of supra-aortic stenosis or stenosis of the coronary ostia; the other patient died at an outside facility, and an autopsy was not performed. A third patient with QTc prolongation sustained a sudden cardiac event but was resuscitated and placed on extracorporeal membrane oxygenation support with ultimate recovery.

Implications of QTc Prolongation in Williams Syndrome

Sudden death: Although documentation of arrhythmia associated with sudden deaths in patients with WS is lack-

ing, the prevalence of QTc prolongation is significantly elevated in patients with WS and increases the risk as in other non-WS groups. Patients with WS are known to have high levels of anxiety and startling because of noises,¹⁴⁻¹⁶ which are associated with sudden death in other patients with known channelopathies.¹⁷ In the few patients in our study who sustained sudden death, QTc prolongation was documented in 60%.¹³ With these limited numbers, a definitive association between QTc prolongation and sudden death in WS cannot be made. However, the possibility is raised that QTc prolongation may be associated with sudden death in WS. Therefore, among other potential causes of death in patients with WS, QTc prolongation with arrhythmic death must be considered. Furthermore, the high prevalence of prolonged QTc in patients with WS highlights the need for further study of causes and mechanisms of sudden death. Moreover, it underlines that other possible causes of sudden death need to be investigated carefully in groups with WS and that broad statements assuming a singular cause based on case report experience, such as made by Burch et al,⁹ should be interpreted with caution.

Attention-deficit hyperactivity disorder (ADHD): Prolongation of the QTc interval in patients with WS is clinically important, because many have ADHD.¹⁸ Because of their ADHD, stimulant medications are pharmacologic mainstays for many of these patients. Significant debate has occurred over the risk for QTc prolongation using stimulants.^{19,20} It is known that variable alterations in the action potential in groups with channelopathies, such as long-QT syndrome or other repolarization syndromes, may increase the risk for ventricular arrhythmias, especially in the presence of adrenergic stimulation.²¹ This information, when coupled with the prevalence of QTc prolongation in patients with WS, has created concern regarding the use of stimulant medications in the treatment of ADHD in these patients. Presently, data are not available to help guide these specific clinical questions; however, extrapolations from the published research regarding other conditions can be made and are covered in the section on management that follows.

Anesthetic risk: Because of the multisystem involvement seen in WS, diagnostic imaging and multiple surgical procedures are common. Frequently, these surgeries and imaging studies, even the most mundane, require anesthesia. The risk for sudden hemodynamic decompensation, often with resultant arrest, in the peri-procedural period in patients with WS is well-known and has been the topic of several reports.^{9,22} Factors previously implicated include severe bilateral outflow tract obstruction, unrecognized coronary ostial stenosis, and severe branch pulmonary artery stenosis with suprasystemic right ventricular pressures. In light of the high prevalence of prolongation of the QTc interval we reported,¹³ it is important to remember that a

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number of anesthetic and periprocedural medications have been found to prolong the QTc interval, including commonly used volatile anesthetics.²³ Scuderi²³ recently noted that there is debate as to the degree of QTc prolongation in the setting of various volatile anesthetics. In their well-designed pharmacologic study of inhaled sevoflurane, Han et al²⁴ clearly demonstrated a marked increase of the QTc interval (46 ms). Given that >13% of patients with WS already have QTc prolongation at baseline of >460 ms,¹³ the administration of sevoflurane in those patients, assuming similar pharmacokinetics, would result in a QTc interval >500 ms, the threshold for high risk in the setting of congenital long-QT syndrome.²⁵

Fentanyl and vecuronium have been shown to be associated with prolongation of the QTc interval at the time of anesthetic induction in patients with coronary artery disease.²⁶ Although most patients with WS who sustain sudden death in the periprocedural period do not have significant atherosclerotic coronary artery disease, they do, as Burch et al⁹ pointed out, have coronary artery pathology, with $\geq 5\%$ having coronary ostial stenosis.⁴ Thus, the possibility that the QTc interval could be prolonged in patients with WS because of the administration of fentanyl and vecuronium should be considered.

Management of QTc Prolongation in Williams Syndrome

Prolongation of the QTc interval in patients with WS should be sought, and appropriate treatment and follow-up should be carefully considered. Although data are not available to support evidence-based recommendations for medication use or avoidance in WS, extrapolations from the published research regarding other conditions can be made. A large number of the patients in our study who had evidence of QTc prolongation had not been treated with β -blocker therapy. Given the increased risk for sudden death in patients with WS, and the increased risk for sudden death in patients with prolongation of the QTc interval, the use of β -blocker therapy in patients with WS may be an appropriate "preventive" intervention to consider. To date, no studies have addressed the use of β -blockers in patients with WS, so any benefit is theoretical and based on previous studies in patients with channelopathies. The effectiveness of β -blocker therapy may be specific to particular mechanisms of QTc prolongation, and therefore, application to the WS population may or may not be beneficial in preventing Torsades de Pointes tachycardia and/or sudden death. Nonetheless, the side effect profile of β -blocker therapy is acceptable, and the risk of use in these patients would be considered low. For these reasons, the initiation of β -blockers may be reasonable and should be considered in any patient with WS with a QTc interval of ≥ 460 ms.

Given the high rate of ADHD in patients with WS,²⁷ the use of ADHD medications will be clinically necessary for many of these patients. Recently, Elia and Vetter²⁸ recommended that ADHD medication prescribing practices in regard to the QTc interval should remain unchanged, and most investigators agree that ADHD medications are of little concern regarding the prolongation of the QTc interval.²⁹ The American Academy of Pediatrics and the Amer-

ican Heart Association have issued a joint statement regarding the CV evaluation of pediatric patients before the initiation of ADHD therapy.¹⁹ The CV evaluation of a patient with WS before the initiation of ADHD medications should be the same as with any other patient who needs treatment, with the caveat that 80% of patients with WS have CV abnormalities.⁴ As recommended by the American Academy of Pediatrics and the American Heart Association statement, all patients should have thorough histories taken and physical examinations performed before the initiation of ADHD medications.¹⁹ Because prolongation of the QTc interval may occur with or without concomitant structural CV abnormalities, all patients with WS should undergo electrocardiographic screening before the initiation of ADHD medications. If electrocardiography demonstrates abnormalities, especially prolongation of the QTc interval >440 ms, referral should be made to a pediatric cardiologist well versed in the care of patients with WS. Assessment should include elucidation of other risk factors for sudden death, review of medications that may contribute to QTc prolongation, and an enhanced adrenergic state. Strong consideration should be given to treatment with β -blocker therapy for those with QTc prolongation before the initiation of ADHD medications. Furthermore, all patients with WS who are maintained on ADHD medications should undergo repeat electrocardiography at appropriate intervals, with or without β -blocker therapy.

A complete discussion on the periprocedural evaluation and management of patients with WS is beyond the scope of this commentary. Patients with WS should undergo CV and electrocardiographic evaluation before sedation and anesthesia. Each patient must be evaluated in the light of individual clinical manifestations and findings. Anesthetic regimens should avoid agents that result in significant decreases in blood pressure or prolongation of the QTc interval. Medley et al²² covered the perioperative management of WS thoroughly, with 1 recommendation that is questioned. In their report, Medley et al²² referenced the recommendation of Horowitz et al³⁰ that "the preoperative work-up should include coronary angiography for all patients with WS requiring anesthetic care." Unfortunately, because of the cognitive and behavioral factors involved, most patients with WS require anesthesia for invasive studies, including coronary angiography. Certainly, careful non-invasive assessment of coronary arterial patency should be used when possible. If catheterization is indicated, manipulation of the coronary arteries by inserting an angiographic coronary catheter, or aortic root injections, should be reserved only for those instances when absolutely required. In these settings, anesthetic management should assume the possible presence of coronary ostial stenosis.

Given the origin of WS, genetic analysis seeking evidence of a mutation for a known channelopathy is likely to be of limited utility at the present time but should be considered on an individual basis. Although Czošek and Berul³¹ reported a patient with WS who was also found to have a KCNH2 point mutation consistent with congenital long-QT syndrome, no other such reports have been published, and there is no genetic explanation as to how WS could be associated with the known channelopathies, as all known mutations are remote from 7q11.23. However,

unique mechanisms for QTc prolongation in WS may be present, making this population an important one to study.

Future Investigations of QTc Prolongation in Williams Syndrome

The finding that the prevalence of QTc prolongation is high in patients with WS represents the first report of electrocardiographic data in patients with WS. Because of that work, interest has developed for a multicenter collaborative effort to explore further the association of QTc prolongation with sudden death in WS. It is hoped that such a study will provide greater insight into not only the effect of QTc prolongation on sudden death, but also the causes of sudden death in patients with WS.

Currently, detailed genetic evaluations of 7q11.23 are planned to determine if a gene encoding a protein involved in cardiac ion channels, especially potassium channels, is present. Mechanisms of prolongation of the QTc interval in patients with WS may also improve understanding of the pathophysiology of prolongation of the QTc interval in patients without WS.

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