Munday et al. Int J Clin Cardiol 2016, 3:072
Volume 3 | Issue 1
ISSN: 2378-2951

International Journal of Clinical Cardiology

Original Article: Open Access

Increased Corrected QT Interval (QTc) in First Nations Women of Northern British Columbia with Systemic Lupus Erythematosus (SLE)

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Abstract

Long QT Syndrome (LQTS), a genetic predisposition to sudden cardiac death is defined by a prolonged corrected QT interval (QTc) measured on electrocardiogram (ECG). A participatory research project has been underway with the Gitxsan of Northern BC for more than ten years where the condition (LQTS1) is common, due to a founder mutation (V205M) in *KCNQ1*. It is effectively treated with beta blockers and avoidance of QT prolonging drugs. Some chronic conditions are also known to increase the QTc, which is an independent risk factor for sudden cardiac death. Autoimmune disease is also common in BC First Nations, and among our study population we noted an enrichment of women with Systemic Lupus Erythematosus (SLE) in categories with a high QTc. Here we assessed whether persons with SLE and without known LQTS mutations, have a higher than expected QTc with implications for clinical management. Our results support an increase in QTc associated with SLE. In addition to congenital LQTS, physicians should be alerted to the risk for an increased QTc with SLE and consider avoidance of QT prolonging medications when possible.

Keywords

Long QT Syndrome, QTc, Autoimmune disease, Systemic lupus erythematosus, First Nations

Introduction

Long QT Syndrome (LQTS), congenital or acquired, is characterized by a prolonged QT interval identified on an electrocardiogram (ECG) predisposing to arrhythmias, ventricular fibrillation, cardiac arrest and sudden death [1]. Congenital LQTS is inherited due to abnormalities in at least 13 known genes (LQTS1-LQTS13) predominantly responsible for ion channel function [2]. Acquired LQTS occurs without a molecularly defined LQTS mutation and may be caused by drugs [3], some cardiac diseases [4] as well as other chronic diseases such as diabetes [5], and rheumatic/autoimmune diseases including systemic lupus erythematosus (SLE) [6] and rheumatoid arthritis [7].

Congenital LQTS is relatively rare, affecting an estimated 1:2000 [8], but it is disproportionately prevalent (~1:120) in a Canadian First Nations community in northern British Columbia (the Gitxsan). Through community initiation, individuals diagnosed with LQTS and their relatives participated in our early studies, which led to the identification of a novel c.613 G > A missense mutation resulting in a valine to methionine substitution at position 205 (V205M) in *KCNQ1*. *KCNQ1* is the gene most commonly associated with LQTS (LQTS1) [9] and encodes the α subunit of the slow delayed rectifier potassium channel, Ik_s. This novel mutation was shown in mechanistic studies to alter Ik_s by slowing activation and accelerating deactivation [10]. Furthermore, a prolonged QTc, cardiac arrest and sudden cardiac death correlates with mutation positive status, supporting that it predisposes individuals to LQTS [10].

A normal QTc is generally considered to be within 390-450 ms for men and within 390-460 ms for women [11]. A prolonged QTc is an independent risk factor for sudden death reflecting repolarization instability, predisposing individuals to cardiac arrhythmias [12,13]. Although the mutation positive patients in our study cohort clearly show a prolonged QTc, an increase in the baseline QTc in the mutation negative group has also been observed [10,14] suggesting other factors, genes and QT prolonging circumstances [15], may contribute to a prolonged QT interval. Further identification of mutations responsible for LQTS, as well as the elucidation of non-genetic contributing factors, is important in the delivery of appropriate clinical management in this community. For this study, we noted an enrichment of women with a diagnosis of SLE, in our category of those with a QTc over 470 ms. This was of interest since SLE has been previously found to be prevalent in British Columbia and in other aboriginal populations [16-18].

SLE is an autoimmune disease of unknown cause that primarily affects young adult women. It causes widespread, nonspecific organ

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Citation: Munday FA, Asuri S, McIntosh S, Jackson H, Tang A, et al. (2016) Increased Corrected QT Interval (QTc) in First Nations Women of Northern British Columbia with Systemic Lupus Erythematosus (SLE). Int J Clin Cardiol 3:072

Received: November 06, 2015: **Accepted:** January 27, 2016: **Published:** January 30, 2016

inflammation, primarily in the kidneys and skin, and more than half of SLE patients exhibit cardiac involvement [19,20]. The inflammatory effects of SLE can impact all parts of the heart including valves, blood vessels, the pericardium and the myocardium. Arrhythmia may result and the QT interval has been noted to be affected [21-23].

The objective of this study was to determine whether SLE patients enrolled in our LQTS study, without the V205M LQTS founder mutation, have an elevated QTc, with implications for management.

Materials and Methods

Long QT syndrome study participants

Community based participatory methods as previously described [10] were adhered to. Community members were invited to participate if they had a diagnosis of LQTS, a possible diagnosis (designated by an increased corrected QT interval) or had a known relative with LQTS. Ethics approval was granted by the UBC and Northern Health Authority ethics boards. The Gitxsan Health Society reviewed and participated in protocol development. Multi-generation family and medical histories were documented by trained genetic counsellors. Medical records were reviewed, an ECG was carried out, and all other ECGs on file were collected for review. As previously reported, blood or saliva samples were collected from the participants under the stipulation of *DNA on Loan* [24]. DNA was extracted by standard protocols. Genotyping was carried out for the known *KCNQ1* V205M mutation and a second *KCNQ1* mutation (R591H) documented in an adjacent community [14] in the BC Provincial Health Services Authority (PHSA) lab of the BC Children's Hospital, Vancouver. In addition, three individuals with SLE with a documented prolonged QTc > 470 ms, but negative targeted V205M mutation testing underwent expanded testing to exclude mutations in the 5 genes most commonly responsible for LQTS (*KCNQ1, KCNE1, KCNH2, KCNE2*, and *SCN5A*). No other mutations were detected.

Participants also completed an interview which documented the presence of chronic disease diagnoses [10]. All participants with a documented previous medical diagnosis of SLE were considered to be 'affected with SLE' and eligible for this sub-study. Those thought to have a 'possible' diagnosis of SLE were excluded. Further eligibility included at least one ECG and completion of targeted *KCNQ1* mutation testing.

Four groups for comparison were established:

1) Those with a documented V205M mutation, n = 26,

2) Those with a confirmed medical diagnosis of SLE, n = 9,

3) First to third degree relatives of those with the V205M mutation but testing negative for the V205M mutation, n = 16 and

4) First to third degree relatives of those with SLE and testing negative for the V205M mutation, n = 23.

Exclusions

Individuals below the age of sixteen years were excluded. All men were also excluded due to low prevalence of SLE among males (n = 2), and the confounding difference in QTc between men and women with the V205M mutation [10]. Furthermore, those with medical co-morbidities that might affect the QTc interval, such as known cardiovascular disease, diabetes and other autoimmune diseases (rheumatoid or other inflammatory arthritis) were excluded. Those with arthritis of unknown etiology were not excluded. Those homozygous for the V205M mutation (n = 4) were also excluded since that group has significantly increased QTc compared to heterozygous carriers [25]. One case that had SLE and the V205M mutation was excluded and 4 cases with a possible or probable diagnosis of SLE that could not be confirmed were also excluded. All relatives greater than 3 degrees of relationship from V205M-positive or SLE individuals were excluded from the control groups.

QTc measurements

Corrected QT (QTc) measurements, blinded to mutation and disease status, were made on all available ECGs (12-lead) for each participant in the study by HJ, under the supervision of AT, an electro physiologist. QTc values were determined using the tangent method [26], Bazett correction [27] and an average RR interval. For each individual, the longest QTc in any lead from all available ECGs was used to determine the study QTc for each participant.

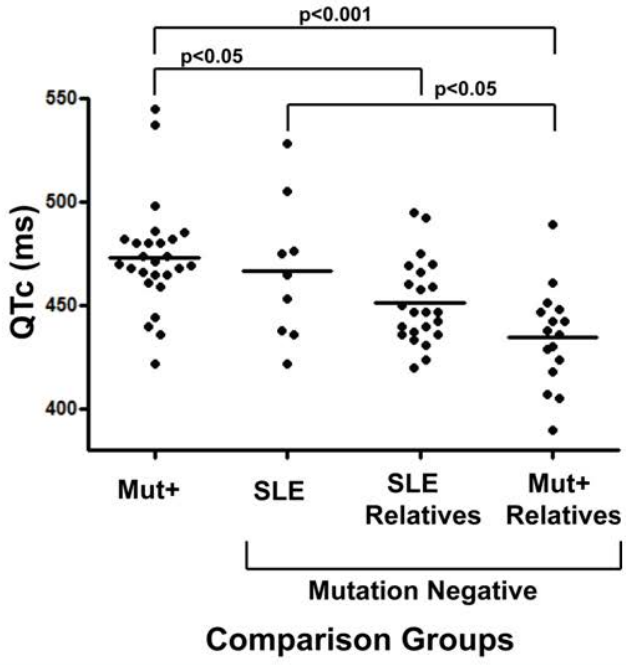

Figure 1: QTc intervals of SLE patients compared to LQTS mutation positive cases and their relatives. From left to right 1). *KCNQ1* V205M mutation positive (mut+) persons without SLE (n = 26), 2). SLE cases (n = 9), 3). Relatives of those with SLE (n = 23) and 4). Relatives of those with the *KCNQ1* V205M mutation (n = 16). All persons are female and have been tested for the LQTS causing mutation, and only those in group 1 are *KCNQ1* V205M mutation positive. SLE, relatives of SLE and relatives of mutation positive are all negative for the *KCNQ1* mutation. Each point represents the highest QTc determination of all ECGs from one individual. The short horizontal bars represent each group's mean QTc. Mean QTc values ± standard deviation of each group, from left to right on x-axis, are: 473.3 ± 26 ms, 466.4 ± 34 ms, 451.0 ± 20 ms and 434.8 ± 24 ms. (QTc: corrected QT interval; SLE: systemic lupus erythematosus).

Statistical analysis

The software program Graphpad Prism was used for all statistical analyses. Two-tailed *t*-test was performed to compare mean QTc values of subgroups. Means with 95% confidence intervals were reported and p values equal to or less than 0.05 was considered statistically significant. One-way ANOVA with Tukey post-test and test for linear trend was used to compare means of multiple groups.

Results

Statistical analysis

The mean ages of participants in each of the groups were: (1) Mutation positive - 49 years (SD ± 15), (2) Affected with SLE - 51 years (SD ± 10), (3) First to third degree relatives of those with the mutation, but testing negative for the mutation - 43 years (SD ± 19) (4) First to third degree relatives of those with SLE, but testing negative for the mutation - 48 years (SD ± 15).

The mean QTc of each of the four groups showed a descending trend (Figure 1): mutation positive individuals had the highest mean QTc (473.3 ± 26 ms) followed by SLE patients (466.4 ± 34 ms), relatives of SLE patients (451 ± 20 ms) and mutation negative individuals related to a mutation positive person (434.8 ± 24 ms). Through ANOVA, the mean QTc values of the groups were significantly different ($p < 0.0001$). Tukey's post-test showed significant difference between: 1) SLE vs. V205M-negative group ($p < 0.05$), 2) V205M-

positive vs. V205M negative group ($p < 0.001$), and 3) V205M negative related to SLE vs. V205M positive group ($p < 0.05$).

Discussion

Systemic lupus erythematosus has been previously reported to occur with increased prevalence in First Nations in Canada and in Native Americans. For example, Atkins et al. [16] reported the prevalence of SLE in the Nuu-Chah-Nulth to be 0.5% [16]. Two subsequent reports have corroborated increased rates – Peschken et al. [17] reported a 42.3/100,000 rate in First Nations and Native Americans, compared to 20.6/100,000 in Canadians Caucasians [17] and in a more recent study, Ferucci et al. [28] from the United States suggest a prevalence of 178/100,000 (0.12%), three times the previous estimation in Native Americans and Alaska Natives [28]. Although the prevalence of SLE is said to be high in the Gitxsan, the overall prevalence has not been determined. Therefore, in our study ascertaining participants based on presumption of LQTS we were surprised that the over-all study population rate of SLE was 4% which is 8 times higher than previous estimates of SLE in First Nations of BC. Furthermore, at the time of the analysis 11% of those with a QTc greater than 470 ms had a diagnosis of SLE. Ascertainment bias based on eligibility of a possible diagnosis of LQTS in our study may have resulted in a disproportionate number of those with SLE entering our study. Considering previous reports suggesting that QTc may be elevated in those with SLE, we set out to determine if that was the case in our study population.

Since the QTc may be influenced by numerous factors [29] we chose our comparison groups as close family based controls of mutation positive LQTS (group 1), and with SLE (group 2), and excluded those with other potential reasons for a prolonged QTc such as the presence of other chronic disease from all case and control groups. Our results support that those participants diagnosed with SLE in the Gitxsan community exhibit an elevated QTc, consistent with previous reports [6,21,30]. Of note, a gradient was observed in the mean QTc of four comparison groups of participants, with the lowest being the mutation negative relatives of those mutation positive and the highest being those with the V205M mutation. Those with SLE had a mean QTc lower than those with the mutation, but not significantly so. In turn, their relatives had a mean QTc lower but not significantly different than those with SLE.

The mechanism for QT interval prolongation in SLE has been the focus of previous research and may be related to the presence of anti-Ro/SSA antibodies. Lazzerini et al. [6] observed a correlation between prolonged QTc and the presence of anti-Ro/SSA antibodies in patients with connective tissue diseases including SLE. They hypothesized an etiological role of anti-Ro/SSA antibodies in increasing risk of arrhythmia [23]. Their hypothesis is supported by the fact that children born to anti-Ro/SSA positive mothers exhibit transient QT interval prolongation [31]. Bourré-Tessier et al. [30] found that anti-Ro/SSA positive SLE patient's exhibit prolonged QTc when compared to anti-Ro/SSA negative SLE patients. It has been hypothesized that cross-reaction between anti-Ro/SSA antibodies and the *KCNH2* delayed rectifier potassium channels (I_{Kr}) in the heart could contribute to a prolonged QT interval by inhibiting I_{Kr} [30,32] much in the same way that *KCNH2* is affected by numerous drugs. LQTS induced by anti-*KCNH2* antibody has been reported in at least one patient [32] when researchers sought to determine the basis of a new diagnosis of LQTS with no known LQTS mutations but the presence of positive anti-SSA/Ro antibodies. A more recent study has supported the hypothesis further by immunizing guinea pigs with the Ro antigen, and demonstrating QT prolongation on ECG after the development of high titers of the anti-Ro antibody [33]. Further in vitro studies in that same study, demonstrated Anti-Ro antibodies inhibited $I_{Kr,}$ explaining the resultant prolonged QT interval [33]. There are other possibilities to consider in that certain drugs used in the treatment of SLE (hydroxychloroquine) may prolong the QTc [23,34,35], and some have suggested the prolonged QTc in SLE could be related to autonomic dysfunction known in SLE. This hypothesis deserves further exploration [36].

The lack of significant difference between the QTc of SLE patients and their relatives is a novel finding and may be due to the presence of autoantibodies and pre-clinical autoimmune disease. Important to also note is that SLE is caused by a poorly understood combination of environmental and genetic factors. Although over 100 candidate genes have been identified in genome wide association and linkage studies [37], the nature of transmission appears to be complex, involving interactions between several genes and their variants [38,39]. Independent of SLE antibodies, other yet to be defined genetic factors predisposing to SLE could also unknowingly affect the QT interval and be present in undiagnosed family members.

The finding that those with SLE are at risk for an increased QTc has management implications for those affected. A prolonged QTc is an independent risk factor for ventricular arrhythmias and sudden cardiac death [1,12,13,40,41] and avoidance of QT prolonging drugs [42] has been proposed to reduce risk [30,33].

Conclusion

Our study supports previous evidence that those with SLE are at risk for a prolonged QTc. This finding has management implications for those affected, especially in First Nations populations where SLE is common. A prolonged QTc is a risk factor for arrhythmia and sudden cardiac death, avoidance of QT prolonging drugs need to be considered. In cases where QT prolonging drugs are necessary for treatment of chronic diseases, such as SLE, regular cardiac monitoring should be considered.

Limitations

Several aspects remain to be addressed by future research. Due to low sample size, men and mutation positive SLE patients were excluded, including one patient with a diagnosis of SLE and LQTS based on the V205M mutation status. History of QT prolonging drugs was reported in each subgroup, however this study did not assess temporal association between QTc and drug use. Furthermore, other genetic variants influencing the QTc may be present in families with SLE. It is possible that SLE and the V205M mutation, and/or other variants could have an additive or synergistic effect on prolongation of the QTc. Future work could examine the influence of anti-Ro/SSA, other autoantibodies, and genetic varaints on the background QTc in this population.

Acknowledgements

We would like to thank the participants of the LQTS project, and the Gitxsan Health Society for their governance and support of this on-going project. This work was partially funded by the Canadian Institutes of Health Research grant number 81197 to L. Arbour period.

Ethics Statement

This study was conducted with the approval of the University of British Columbia and Northern Health Authority ethics boards and adhered to ethical standards. This study was carried out in a participatory manner in collaboration with the Gitxsan Health Society Board.

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