Bulletin of the IACFS/ME
A Quarterly Publication of the International Association for CFS/ME

Brief Report

Shortened QTc interval in chronic fatigue syndrome

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Funding: ME Research UK, Irish ME Trust, John Richardson Research Group, CFS/ME Northern Clinical Network.

None of the funders contributed to the design, performance or interpretation of the results of this study.

None of the authors have any conflict of interest.

Abstract

Chronic fatigue syndrome (CFS) is a common, debilitating disease that is frequently associated with autonomic dysfunction. One previous study of a selected population using a manual measurement technique suggested CFS is associated with a shortened QTc interval. Here we assessed QTc in a large UK population of CFS patients using automated, clinically applicable, measurement techniques and confirmed that QTc is significantly shortened in CFS patients compared to non-CFS fatigued and control populations. Automated measurement of QTc in clinical practise has potential utility as a diagnostic biomarker in CFS.

Key words: chronic fatigue syndrome; qtc; electrocardiogram

Introduction

Chronic Fatigue Syndrome (CFS) is a disease (prevalence 0.2-4%)[1], characterised by persistent/recurrent post-exertional fatigue that cannot be explained by other conditions, and is present for longer than 6 months [2,3]. Despite having such a high prevalence, the underlying mechanisms that lead to CFS remain poorly understood [1] and there is no biological marker available for diagnosis.

Autonomic dysfunction is considered to be a potential aetiological factor in CFS. Autonomic symptoms are present in almost 90% of those with CFS and its presence correlates with fatigue severity [5,6]. The QT interval on the surface electrocardiogram (ECG) may be influenced by the autonomic nervous system with one study suggesting that the corrected QT interval (QTc) is shortened in those with CFS compared to controls. This study however examined the prevalence of QTc in a selected group of CFS patients (referred for investigation of occult dysautonomia or syncope) using a manual measurement technique [7]. In this study we set out to confirm the findings of the previous study, but using an automated QTc assessment technique appropriate to clinical practise applied to an unselected population.

Method

All patients referred to the Northern Regional CFS Clinical Service based at the Royal Victoria Infirmary (Newcastle Upon Tyne, UK) between November 2009 and January 2012 were included in the study. 12 lead ECG is performed as a routine assessment in all patients attending the clinic.

Subjects also routinely complete the Orthostatic Grading Scale (OGS), a fully validated self-report assessment tool for the symptoms of orthostatic intolerance due to orthostatic hypotension (e.g., severity, frequency, and interference with daily activities) which consists

of 5 items, each graded on a scale of 0 to 4 [8]. Adding the scores for the individual items creates a total score and the chalder fatigue scale.

All ECGs were anonymised. They were assessed for rhythm, atrioventricular conduction, ventricular conduction and repolarisation abnormalities, and for any signs of ventricular enlargement or previous/current ischaemic events using a standard proforma. These interpretations were discussed with, and confirmed by, a consultant cardiologist. All interpreters were blinded to the diagnoses of the patients. Heart rate and PR/QRS/QT/QTc intervals were calculated automatically for all ECGs using a *Philips PageWriter Trim II Cardiograph*.

For comparative use, the ECGs from 50 non-fatigued controls – referred to the Royal Victoria Infirmary's Falls and Syncope Service for problems with balance or dizziness – were anonymised and interpreted using the same method.

Approval

The research undertaken was approved by the Newcastle and North Tyneside ethics committee and was funded by ME Research UK.

Statistical Analysis

All data was analysed to determine whether it followed a Gaussian distribution. The mean values and standard deviations were calculated for heart rate (HR), QRS distance (QRSD), and PR/QT/QTc intervals in all groups and were compared using ANOVA (analysis of variance). The correlation between these values and patients' OGS scores were analysed using Pearson's test. The proportions of those with electrical and structural cardiac abnormalities were compared between all groups using Chi-squared analysis. P values < 0.05 were considered significant.

Results

220 patients referred for fatigue were included in the study. One hundred and seventy seven of these were found to fulfil the diagnostic criteria for CFS [3], whilst 43 were assigned alternative diagnoses responsible for their fatigue. None of the subjects were taking medication that could have affected the QT interval.

ECG Abnormalities & Measurements

No significant difference was found when comparing structural and electrical cardiac abnormalities in CFS patients to non-CFS fatigued patients and controls (**Table 1**). There were also no significant differences in HR, PR, QRSD or QT intervals between the groups, however, the QTc interval was found to be significantly shorter in CFS patients compared to controls (**Figure1a**).

Screening Scores and ECG Measurements

As would be expected, higher autonomic symptom burden assess by OGS scores correlated with an increase in HR ($p=0.0004$;$r2=0.1$). A higher OGS score also correlated with shortened QT intervals (**Figure 1b**). Although no significant correlation was found when QT intervals were corrected.

Discussion

This study has provided further evidence that CFS patients have QTc intervals that are significantly shorter than non-fatigued individuals confirming the findings of the previous small study [7]. The current study analysed ECG tracings from four times as many CFS patients in an unselected manner. We would suggest that the QTc interval has the potential to be a diagnostic tool in CFS diagnosis, although there was no statistically significant difference between the average QTc intervals in the CFS compared to the non-CFS fatigued group, overall the QTc intervals were shorter. We would suggest however further prospective studies are needed with optimised equipment to determine whether this may be a fatigue specific, or a CFS specific phenomenon. Due to the large spread of QTc intervals in this study, it is possible that the QTc interval would prove more useful in combination with other tools in separating CFS patients from healthy individuals.

Recent studies have identified the specific genetic abnormality now known as short QT syndrome. This is recognised as a specific cardiac channel abnormality which is associated with sudden cardiac death in young people. It is diagnosed when the QTc is >310 msecs. The short QTC syndrome may well be similar to the long QTc where increased recognition of the condition is associated with the appreciation of the syndrome as heterogeneous. Currently abnormalities of cardiac channels tend to be documented post mortem, it is perhaps possible that there are more subtle abnormalities of conduction that lead to disability rather than death, which will become recognised as our knowledge of genetic susceptibility in a chronic disease setting is improved.

CFS is a disease that usually affects younger individuals and is uncommon in over 65s. The patients included in this study were young compared to the normal controls, therefore it is unsurprising that we show that ECG traces in CFS patients display no more significant structural or electrical abnormalities compared to healthy controls or non-CFS fatigued patients.

Although autonomic symptoms (OGS score) did not correlate with QTc, our finding of a significant relationship between increasing HR and worsening autonomic symptoms points to potential therapeutic targets. It is possible that lowering the HR of patients in this and other groups may act to reduce the severity of symptoms associated with AD. This has the potential to be of huge benefit in those who are affected by the condition.

This study was not without its limitations. This was a retrospective review of ECG collated from patients attending our clinical service, we did not consider intra-patient variability of the QTc or whether the equipment used in our clinic is optimised for calculating QTc. Discrepancies in the groups' age and sex characteristics are a potential confounder. Due to the nature of the cohort, the non CFS-fatigued group was small, with only 43 members. This makes comparison between these patients and CFS patients difficult.

In conclusion, more research is needed into this field. Only with further research could the validity of the QTc interval and its use in the diagnosis of CFS be assessed. Such research could be used to define a cut-off point between healthy individuals and fatigued individuals. Further research should also aim to determine whether the relationship between CFS and QTc intervals is causative or simply correlative.

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Table 1. ECG abnormalities in CFS, non-CFS fatigued and control groups

	CFS (n=177)	Non-CFS Fatigued (n=43)	Normal (n=50)	*p* Value
Age [Mean +/- SD]	40.3 +/- 13.4	44.9 +/- 13.7	69.3 +/- 12.7	
Male **[n (%)]**	32 (18)	13 (29)	12 (24)	
QT [Mean +/- SD]	369 +/- 26	374 +/- 31	383 +/- 31	0.02
QTc [Mean +/- SD]	403 +/- 19	414 +/- 22	417 +/- 34	0.0084
Chalder fatigue score [Mean +/- SD]	9.0 +/- 3	9.3 +/- 2	-	n.s
ECG Abnormality [n (%)]				
Sinus Arrhythmia	27 (15)	4 (10)	5 (10)	n.s.
Sinus Arrhythmia with Ventricular Ectopics	0 (0)	0 (0)	1 (2)	n.s.
Atrial Fibrillation	0 (0)	0 (0)	1 (2)	n.s.
1st Degree Heart Block	0 (0)	3 (14)	3 (6)	n.s.
Left Axis Deviation	0 (0)	0 (0)	1 (2)	n.s.
Right Axis Deviation	1 (1)	0 (0)	0 (0)	n.s.
Q Waves - Anterior Leads	0 (0)	0 (0)	2 (4)	n.s.
Ventricular Conduction Defect				
Incomplete RBBB	32 (18)	6 (19)	5 (10)	n.s.
VCD Not Otherwise Specified	9 (5)	4 (10)	2 (4)	n.s.
Left Ventricular Hypertrophy	1 (1)	0 (0)	2 (4)	n.s.
ST Depression				
Anterolateral	5 (3)	2 (5)	0 (0)	n.s.
Inferolateral	1 (1)	0	1 (2)	n.s.
T Wave Abnormality				
Anterior	0 (0)	4 (10)	2 (4)	n.s.
Anterolateral	1 (1)	0	2 (4)	n.s.

Figures

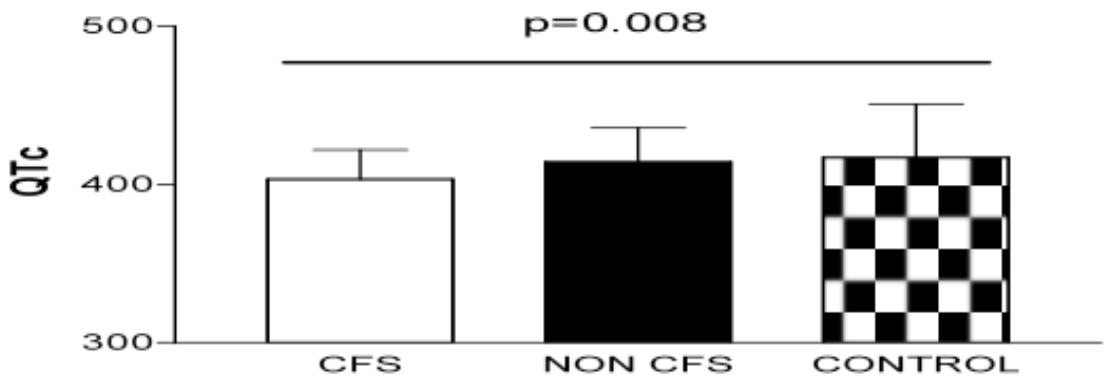

Figure 1a. QTc interval (ms) changes in CFS, non-CFS fatigued and control groups

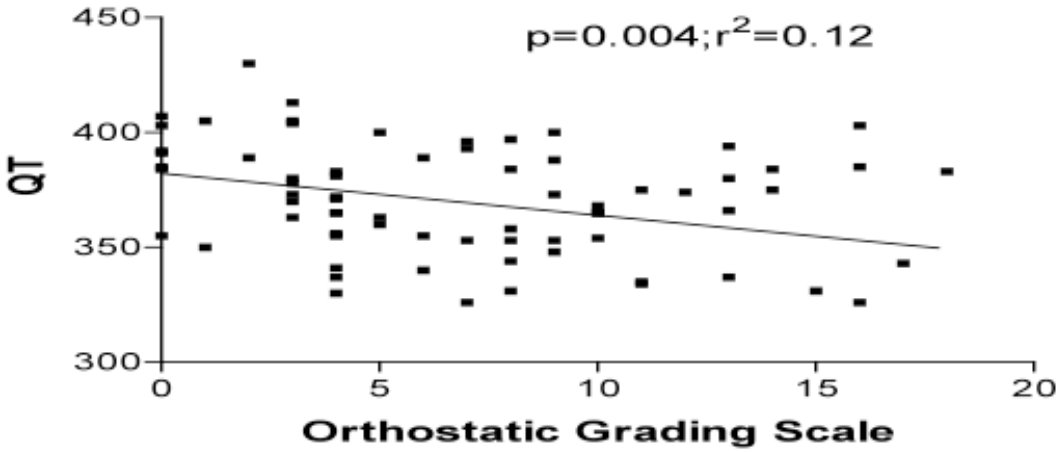

Figure 1b. Graph showing correlation between QT interval (ms) and OGS score.

Bulletin of the IACFS/ME. 2012;19(3/4): 202-211. © 2012 IACFS/ME