QT Variability in Amyloidosis of Familial Mediterranean Fever

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ABSTRACT: **Background:** The association between familial Mediterranean fever (FMF) and increased risk for ventricular arrhythmias is controversial, and data on this subject are meager.
Objectives: To evaluate QT variability index (QTVI) and other repolarization markers associated with arrhythmogenity in patients with amyloidosis of FMF.
Methods: The study group comprised 12 FMF patients with amyloidosis, and 14 age and gender-matched healthy subjects served as the control group. QT measurements were conducted according to accepted procedure, using computerized software for recording and analysis.
Results: No differences were found in clinical and demographic parameters in the study and control groups, except for hypertension which was more common in the FMF amyloidosis group. QTc and power spectral analysis of QT variability parameters were similar in both groups. Nevertheless, QTVI values in FMF amyloidosis patients were significantly higher than in healthy individuals (-1.02 ± 0.38, vs. -1.36 ± 0.32 respectively, $P = 0.02$).
Conclusions: Compared with healthy controls, amyloidosis of FMF is associated with increased QTVI. It remains unknown whether this finding is solely amyloidosis related and whether it has any prognostic significance.

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KEY WORDS: familial Mediterranean fever (FMF), amyloidosis, QT dispersion (QTd), QT variability index (QTVI), arrhythmia

Familial Mediterranean fever is a recessively inherited genetic disease affecting Jews of African and Asian origin, Turks, Arabs, and Armenians. Clinically, it is usually characterized by recurrent and self-limited attacks of fever and pain, involving the abdomen, chest and joints [1]. The disease is associated with mutations in the MEditerranean FeVer (*MEFV*) gene, encoding pyrin, an inflammation-associated protein, which also plays a role in apoptosis [2-4]. The most devastating complication of FMF is AA amyloidosis, which may lead to end-stage renal disease. Colchicine treatment prevents FMF attacks and evolvement of amyloidosis [5].

The association between FMF and susceptibility to arrhythmias remains controversial. Higher than normal QT dispersion (QTd) is an electrocardiographic marker that may by used to identify predisposition for ventricular arrhythmias in high risk patients. QTd is calculated by subtracting the minimal from the maximal QT interval lengths measured for a single beat on a 12 lead ECG [6]. A controversy exists as to the association between increased QTd values and FMF [6-8]. QT variability index is another ECG marker, developed for cardiac risk stratification. It was found that cardiac diseases are associated with increased QT variability, and high QTVI values may indicate an increased risk for arrhythmias [9,10]. The status of QTVI in FMF is not known. In a former study we found normal QTVI parameters in uncomplicated FMF [11]. Given the paucity of knowledge regarding repolarization in FMF in general, and QTVI in FMF in particular, we sought to further evaluate QTVI in FMF.

PATIENTS AND METHODS

A comparative cross-sectional study design was used. The research protocol was approved by the Institutional Review Board. All participants gave a written informed consent.

The study group included 12 patients (5 females) diagnosed with FMF according to accepted criteria [1] and recruited from the outpatient clinic of the national center for FMF, Sheba Medical Center, Tel Hashomer, Israel. Amyloidosis was diagnosed based on renal or rectal biopsy findings. Mean duration of time elapsed from diagnosis of amyloidosis was 24.4 ± 13.3 years. Six patients underwent renal transplantation 9.8 ± 9.1 years earlier, the other six had developed end-stage kidney disease, two of whom underwent continuous hemodialysis. In this group of end-stage kidney disease patients the mean creatinine level was 2.61 ± 0.32 mg/dl, 24 hour urinary protein excretion 3253.0 ± 2323.5 mg/24 hr, and mean creatinine clearance 26.2 ± 3.0 ml/min. In the transplanted patients, the mean

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FMF = Familial Mediterranean fever
QTVI = QT variability index

creatinine level was 1.3 ± 0.6 mg/dl, mean 24 hours urinary protein excretion 718.8 ± 754.9 mg/24 hr, and mean creatinine clearance 65.9 ± 46.4 ml/min. In the whole FMF amyloidosis group the colchicine dosage ranged from 0.5 mg/day to 2.5 mg/day. All FMF patients had been attack-free for at least one week prior to the study.

Fourteen healthy subjects matched for gender and age served as controls. None of the patients or control subjects was taking medications known to influence QT interval duration or repolarization.

PROCEDURE

Participants were asked to avoid smoking, drinking caffeinated or alcoholic beverages for 6 hours prior to the test and strenuous exercise for 24 hours. The test was conducted between 9:00 a.m. and 1:00 p.m. to avoid circadian influences on the electrocardiograms. Room temperature was maintained at 21-23°C.

Participants were instructed to lie motionless in a supine position for 10 minutes. Electrodes were placed in anatomical positions according to standard procedure. Five-minute ECG strips were recorded with a standard device at a sampling rate of 2000 Hz. ECGs with technical errors or inadequate quality were repeated. Moreover, since abnormal depolarization might be associated with abnormal repolarization (although the influence on repolarization parameters is not fully understood), ECGs with bundle block and altered depolarization were excluded. Data were saved in a binary format and processed with custom-made computer software, validated and tested for reproducibility. RR interval was measured between two consecutive beats. QT interval was measured according to accepted standards [12]. Mean QT interval and QT variance (QTv), mean RR interval and RR variability (RRv), were computed from the respective time series [13]. Corrected QT was calculated for all patients using Bazett's Formula. Power spectral analysis was conducted, using the non-parametric fast Fourier transform. Calculations were made in absolute values of power (ms^2). The spectral components were categorized as very low frequency (0.003–0.04 Hz), low frequency (0.04–0.15 Hz), and high frequency (0.15–0.4 Hz). Total power was computed as well.

QTVI was computed by a log ratio adjusted to RR interval, according to the following equation:

$$QTVI = \log_{10}\left[\frac{QTv / QTm^2}{RRv / RRm^2}\right]$$

STATISTICAL ANALYSIS

Data were analyzed with JMP version 7.0 (SAS Institute, Cary, NC, USA). Results are presented as mean and standard deviations. Abnormal results were defined as more than 2 standard deviations from the normal range. Findings were compared between the groups by the Kruskal-Wallis one-way analysis test, and Fisher's exact test for categorical data. A *P* value < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics of the patient groups are outlined in Table 1. The mean age was 54.1 ± 13.4 years for the FMF amyloidosis group and 44.3 ± 10.8 years for the unaffected group ($P > 0.05$). There was no significant difference in gender distribution, height, weight, body mass index, smoking rate, or presence of diabetes mellitus (found only in one FMF patient). Dyslipidemia was similarly found in both groups, although the control subjects had only mild dyslipidemia for which no pharmacological intervention was prescribed. Hypertension was significantly more common in FMF patients (5 patients, 41.67%) but was well controlled in all patients. None of the patients or control subjects had a history of cardiac disease or myocardial infarction.

The calculated QT dynamic parameters for the two groups are summarized in Table 2. There was no difference between the groups in QTm, QTc, and RRm. Power spectral analysis

QTm = mean QT interval
QTc = corrected QT interval
RRm = mean RR interval

Table 1. Clinical characteristics of FMF amyloidosis patients

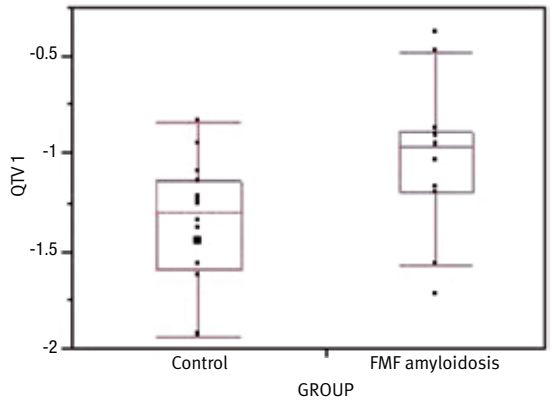
	FMF amyloidosis (N=12)	Subjects without FMF (N=14)	*P* value
Age (yrs)	54.1 ± 13.4	44.3 ± 10.8	NS
M/F	7/5	7/7	NS
Height (m)	1.76 ± 0.08	1.70 ± 0.10	NS
Weight (kg)	66.6 ± 2.1	71.5 ± 14.1	NS
Body mass index (kg/m^2)	23.9 ± 4.5	24.4 ± 3.0	NS
Smokers (%)	16.67	21.43	NS
S/P myocardial infarction (%)	0	0	NS
Diabetes mellitus (%)	8.33	0	NS
Hypertension (%)	41.67	0	0.02
Dyslipidemia (%)	25.00	28.57	NS

Table 2. Clinical characteristics of FMF amyloidosis patients

	FMF amyloidosis (N=12)	Subjects without FMF (N=14)	*P* value
QTc (ms)	417.1 ± 41.3	422.4 ± 27.9	NS
RRm (ms)	816.2 ± 66.3	773.6 ± 86.2	NS
QTm (ms)	376.2 ± 36.9	370.4 ± 23.7	NS
QTVI	-1.02 ± 0.38	-1.36 ± 0.32	0.02
QT – VLF (ms^2)	66.6 ± 31.3	95.9 ± 42.9	NS
QT – LF (ms^2)	103.7 ± 35.3	95.1 ± 24.0	NS
QT – HF (ms^2)	230.1 ± 36.3	214.8 ± 73.7	NS
QT – total power (ms^2)	429.6 ± 50.7	462.0 ± 86.0	NS

QTc = corrected QT interval, RRm = mean RR interval, QTm = mean QT interval, QTVI = QT variability index, VLF = very low frequency, LF = low frequency, HF = high frequency

Figure 1. QTVI distributions in control subjects and FMF amylodosis patients. The black dots represent raw values. In these and subsequent box plots, the central line represents the distribution median; the box spans from 25 to 75 percentile points.



revealed no statistically significant difference in very low frequency, low frequency, high frequency, or total power between the groups. Nevertheless, QTVI results were significantly higher in FMF amyloidosis compared with unaffected patients. The results of QTVI in the control group were similar to those previously published in healthy adults [13,14]. Figure 1 demonstrates the distribution of QTVI results in FMF amyloidosis patients and in controls. The mean QTVI results in the FMF amyloidosis patients who underwent renal transplantation was -1.15 ± 0.31, comparable with -0.96 ± 0.48 for the FMF amyloidosis patients who had end-stage renal disease ($P > 0.05$).

DISCUSSION

The association between abnormal cardiac repolarization and FMF is an emerging medical controversy. The present study, aiming at an evaluation of QTVI, an electrocardiographic marker for cardiac arrhythmogenity, revealed higher QTVI values in FMF amyloidosis patients compared with normal individuals, possibly implying an increased risk for QT interval dysregulation in the FMF amyloidosis group. Recently we reported that QTd, another marker of cardiac arrhythmogenity, appears to be normal in FMF, regardless of AA amyloidosis [6,7]. The present finding suggests that QTVI is a more sensitive parameter to detect QT changes in FMF amyloidosis. The reason for our finding and its clinical implications remain unknown.

With respect to the pathogenesis, the FMF amyloidosis patients had a higher rate of hypertension compared with the healthy volunteers. It is possible that the higher QTVI values in FMF amyloidosis result from the effect of sustained hypertension on the heart. Indeed, hypertension was found to be associated with increased QTVI values [15]. Nevertheless, none of our patients fulfilled the Sokolow-Lyon ECG criteria for left ventricular hypertrophy, and a good blood pressure control was maintained in all, making this possibility dubious.

FMF amyloidosis is associated with renal function impairment. It is well recognized that chronic renal failure (in patients with multiple cardiovascular risk factors) is associated with increased QTVI values [16]. Yet, in the present study, the mean QTVI value in the six patients with end-stage renal disease was statistically comparable (although higher) to that of the six kidney-transplanted patients in whom kidney function was only slightly abnormal (-0.96 ± 0.48 vs. -1.15 ± 0.31 respectively, $P > 0.05$), suggesting that renal function impairment might contribute to, but cannot solely underlie, our finding.

In the current study design, we did not directly evaluate the presence of cardiac amyloidosis. Therefore, although AA amyloidosis rarely involves the heart [17], it remains unknown whether the higher than normal QTVI in FMF amyloidosis in our study group can be attributed to subclinical cardiac involvement with amyloidosis.

Repolarization is affected by the autonomic nervous system. Some researchers suggested that subclinical dysautonomia is common in FMF, regardless of the presence of amyloidosis [18]. Recently however, we found normal heart rate variability parameters and cardiac response to autonomic stimuli in uncomplicated FMF [19,20], but significantly lower heart rate variability results in FMF amyloidosis [21]. This finding suggests that in FMF amyloidosis, dysautonomia might be present and, therefore, the higher QTVI results found in the present study in our FMF amyloidosis patients may be attributed, at least in part, to dysautonomia.

The clinical significance of the higher than normal QTVI values is complex, as no definitive cutoff was set to distinguish normal from abnormal results. Haigney et al. [22] reported that myocardial arrhythmias had developed in patients with a mean QTVI value of -0.80 ± 0.56. Piccirillo and co-authors [23] reported a significantly increased risk for mortality in patients with QTVI values ≥ -0.47. The QTVI results in both the FMF amyloidosis and the control group were lower than the reported values, possibly suggestive of no increased risk for arrhythmias in FMF amyloidosis, despite higher than normal QTVI. Importantly, QTVI results higher than, or similar to, those found in our FMF amyloidosis patients were reported in healthy controls by some authors [24,25]. Therefore, it seems that there is a large range of QTVI values in healthy individuals, overlapping those found in a variety of morbid conditions.

A limitation was that the study group of amyloidosis patients was relatively small, thus limiting the strength of the current study. However, in the colchicine era, recruitment of amyloidosis patients has become a real challenge.

QTd = QT dispersion

CONCLUSIONS

Amyloidosis of FMF is associated with increased QTVI, compared with controls. However, the underlying cause and prognostic implications of this finding remain unknown. Further research and long-term follow-up are required to answer these questions.

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