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Original Article

Late ventricular potentials in familial Mediterranean fever with and without AA amyloidosis

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Abstract

Objective: Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by episodic and chronic inflammation that may lead to both accelerated coronary atherosclerosis and cardiac AA amyloidosis. We hypothesized that late ventricular potentials (LPs), an established electrocardiographic susceptibility marker of ventricular arrhythmias, will be more common in FMF than in the adjusted normal population due to these two types of inflammation-associated cardiac effects. Therefore, we aimed to evaluate the occurrence of LPs in FMF patients with and without amyloidosis.

Material and Methods: Signal-averaged electrocardiography was performed in consecutive patients with FMF using the Frank corrected orthogonal lead system. At least 200 consecutive beats were digitally recorded and averaged, and the presence of LPs was determined according to acceptable thresholds.

Results: There were 54 patients with colchicine-treated FMF, of whom 14 had biopsy-proven AA amyloidosis. None of the uncomplicated FMF patients and 2 of the 14 FMF amyloidosis patients had abnormal or borderline LPs.

Conclusion: Based on LPs as a susceptibility marker for arrhythmia, FMF patients, including the large majority of FMF patients with amyloidosis, are seemingly not at an increased risk to develop arrhythmias.

Keywords: AA Amyloidosis, familial Mediterranean fever, late ventricular potentials, signal averaged ECG, electrocardiography, colchicine

Introduction

Familial Mediterranean fever (FMF) is the most common inherited periodic autoinflammatory illness, affecting a patient population estimated at 120,000 worldwide, mostly of a Mediterranean origin (1, 2). Clinically, FMF is characterized by self-limited attacks of severe inflammation with fever and sterile serositis, each lasting up to 4 days (3-6). Chronic inflammation and its sequelae, including anemia, splenomegaly, continuously elevated acute-phase reactants, and amyloidosis may also occur in 30–60% of untreated or treatment-refractory patients (7). The MEditerranean FeVer gene (*MEFV*) was cloned in 1997, but only recently was it found that the protein encoded by it (pyrin/marenostrin) is a sensor protein of bacterial antigens that is used to promote inflammation (8, 9). Mutations in *MEFV* with enhance this function and allow for episodic and continuous inflammation to occur without interruption and to exert its toll.

AA amyloidosis is the most devastating complication of FMF (7). Despite colchicine prophylaxis, amyloidosis may still prevail in about 5% of FMF patients, leading eventually to end-stage kidney disease in almost all patients. Cardiac involvement in AA amyloidosis is rare and occurs late in the course of amyloidosis, suggesting that most affected individuals may fit into a subclinical stage. Ischemic cardiovascular disease, another adverse outcome of chronic inflammation, may also occur in FMF, as was reported for other diseases associated with a high inflammatory burden such as rheumatoid arthritis, psoriatic arthritis, and other inflammatory disease (10, 11). Higher than normal prevalence of various markers, denoting likelihoods to develop ischemic heart disease, exist in FMF and further support this notion (12). Altogether, it might be inferred that subtle cardiac amyloid deposition and latent coronary disease may occur in FMF and manifest with increased propensity for rhythm and conduction disturbances.

Data on increased rhythm and conduction disturbances in FMF are limited and conflicting. For instance, Akcay et al. (13) found that QT dispersion (QTd) and corrected dispersion (QTcd), which reflect cardiac repolarization heterogeneity and thereby suggest predisposition for cardiac arrhythmias, are increased in uncomplicated FMF. However, different methodologies have yielded normal QTd results in both uncomplicated and amyloidosis-affected FMF patients (14, 15). Limited information is found on depolarization-associated markers for arrhythmias. Low-amplitude, high-frequency waves–termed late ventricular potentials (LPs)–can be detected immediately adjacent to the QRS complex by signal-averaged electrocardiography

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(SAECG) (16, 17). LPs result from intra-ventricular conduction disturbances during depolarization and therefore predispose for reentrant ventricular tachyarrhythmias. Abnormal LPs have been reported to occur in several types of systemic amyloidosis, and were predictive of early death in AL amyloidosis with cardiac involvement (18, 19). Similarly, abnormal LPs were reported in patients with coronary heart disease who developed ventricular arrhythmias, while the absence of abnormal LPs negatively predicted future ventricular arrhythmias or sudden cardiac death (16, 17). Despite the possible risk for increased LPs resulting from ongoing inflammation, to the best of our knowledge the presence of abnormal LPs and their clinical significance have not previously been studied in FMF patients with or without amyloidosis.

Material and Methods

Study design

We hypothesized that uncomplicated FMF patients who are asymptomatic with regard to cardiovascular manifestations may nevertheless manifest increased rate of abnormal LPs, thus reflecting subtle amyloid deposits and subclinical coronary disease. FMF patients with clinically overt AA amyloidosis were a fortiori expected to display abnormal LPs. To test these hypotheses, we performed a cross-sectional analysis in which an unselected subset of FMF patients with and without amyloidosis, followed in our FMF dedicated clinic, were invited (after instructed preparations) to undergo an SAECG test for the detection of LPs.

Study outcome

Detection of abnormal LP tracings in the studied population compared to accepted reference values used to define an abnormal LP result (17).

Study patients and inclusion and exclusion criteria

Patients were recruited from the FMF outpatient clinic of the National Center for FMF, located at the Sheba Medical Center, Tel Hashomer, Israel. To avoid bias, recruitment was sequential according to the order of arrival to the annual or semi-annual follow up visit. Following agreement to participate, patients were scheduled to undergo the SAECG testing and received instructions for preparation. To be included, a patient had to be older than 18 years, meet the criteria for diagnosis of FMF (2), and sign an informed consent. Patients were excluded if they suffered from any known form of cardiac disease. Risk factors for ischemic coronary disease were not used as exclusion criteria. Amyloidosis patients were included only if their AA amyloidosis was biopsy proven using immunohistochemistry in which amyloid deposits stained positive with antibodies to Amyloid A and negative to the major types of other amyloid-forming proteins such as light chains, transthyretin, and others. Patients arriving to the SAECG testing without appropriate preparation or following an attack within the previous 3 days were rescheduled for another test. The study received approval of the local Institutional Review Board. All participants signed a written informed consent.

SAECG testing and determination of abnormal LPs

Participants were asked not to smoke, drink caffeinated beverages, or take other stimulants starting 3 h prior to the test and to avoid strenuous exercise for 24 h prior to the test. They were also asked to discontinue any drugs that might influence the ECG at least 12 h prior to the study. In all cases, the test was conducted between 9:00 a.m. and 12:00 a.m. Room temperature was maintained at 21–23°C. Before starting the test, participants were asked to lie motionless for 10 min.

Late ventricular potentials measurements were conducted with designated computer software (Late Potentials software version 5.0.33, Norav Medical, Yokne'am, Israel). The subject's skin was cleansed with alcohol prior to electrode attachment to decrease noise level to less than 0.7 μV. Leads were positioned according to the Frank corrected orthogonal lead system, representing the X, Y, and Z bipolar axes. At least 200 consecutive beats were digitally recorded and averaged. A commercial algorithm was used to calculate the following parameters: 1) duration of filtered QRS complex (fQRS); 2) root-mean-square voltage of the terminal 40 ms (RMS40); and 3) time during which the low-amplitude QRS signal (LAS) remained below 40 μV. LP measurements were considered abnormal when two of the following criteria were met: 1) fQRS duration >114 ms; 2) RMS40 <20 μV; 3) LAS duration >38 ms (17).

Statistical analysis

Data were analyzed with Microsoft Excel version 2010 (Microsoft Corp.; Seattle, WA, USA) and JMP version 7.0 (SAS Institute; Cary, NC, USA). Results are presented as means and standard deviations. The measured LPs were defined as normal and abnormal using the above criteria and were compared between the amyloidosis and non-amyloidosis groups by Fisher's exact test and Student's t-test. A p value of less than 0.05 was considered statistically significant.

Results

The total study group comprised 54 patients. All received colchicine treatment at a mean dose of 1.74±0.70 mg/day. Forty patients with repeatedly normal urine analyses formed the uncomplicated FMF subgroup. The other 14 patients had biopsy-proven AA amyloidosis. Of the 40 patients with uncomplicated FMF, 7 were obese, 4 were smokers, 4 had essential hypertension (well controlled with treatment), and 7 had treatment-responsive dyslipidemia. None of the patients had diabetes, but 3 had other co-morbidities (Behçet's disease, treated hypothyroidism, and Parkinson's disease). None of the patients had a history of ischemic heart disease or myocardial infarction, but 12 had a family history of heart disease. Of the 14 patients with amyloidosis, 6 underwent renal transplantation, 1 was treated with continuous dialysis, 4 had proteinuria, and 3 had nephrotic syndrome. Additionally, 10 of the FMF patients with secondary amyloidosis had one or more cardiovascular risk factors (Table 1). Two patients with amyloidosis had a past history of myocardial infarction, but nevertheless were enrolled due to inactive cardiac disease and a too small cohort with FMF amyloidosis. The patients with renal amyloidosis were significantly older than the patients without amyloidosis (50.1±15.8 years vs. 38.6±17.7 years; p=0.038).

None of the patients with uncomplicated FMF had abnormal LPs. The SAECG results and clinical data of the 14 patients with renal amyloidosis are presented in Table 1. Two patients had abnormal or borderline LPs (p=0.06 compared with the non-amyloidosis group), and they are presented below.

Patient 13 in Table 1, who displayed abnormal LPs, was a 71-year-old female with several cardiovascular risk factors (advanced age, obesity, hypertension, dyslipidemia) who had undergone renal transplantation for AA amyloidosis kidney disease at age 65. Blood pressure values and dyslipidemia were well controlled by medications. A recent echocardiogram demonstrated normal cardiac systolic function, no signs of relaxation abnormalities, and mild mitral and tricuspid regurgitations. She also had hypothyroidism treated with eltroxin. There was no history of ischemic heart disease.

Patient 14 in Table 1, who also displayed abnormal LPs, was an 81-year-old Ashkenazi male whose amyloidosis resulted in nephrotic syndrome. His LP values were of borderline results (RMS40=19, LAS duration under 40 μV=38). Two years prior to the study, he had a myocardial infarction that was treated with coronary angioplasty. He also had several cardiovascular risk factors (advanced age,

Table 1. Signal-averaged ECG in 14 patients with FMF and renal amyloidosis

Patient #	Age (y)	Sex	Clinical condition	Cardiovascular risk factors	Status post myocardial infarction	fQRS duration (ms)	RMS40 (μV)	LAS duration under 40 μV (ms)	Abnormal LPs result
1	28	F	Proteinuria	None	No	79	88	33	No
2	30	M	Dialysis	Positive family history	No	87	45	37	No
3	33	F	Proteinuria	Positive family history, hypertension	No	89	23	33	No
4	40	M	Nephrotic syndrome	None	No	66	110	19	No
5	45	M	Proteinuria	Positive family history	No	94	22	21	No
6	46	M	Nephrotic syndrome	None	No	73	98	17	No
7	48	M	Proteinuria	Obesity, hypertension	No	82	30	28	No
8	49	M	s/p renal transplantation at age 27	Positive family history	Age 47	80	79	19	No
9	49	F	s/p renal transplantation at age 46	Positive family history, hypertension	No	88	27	35	No
10	50	F	s/p renal transplantation at age 29	None	No	76	57	23	No
11	60	M	s/p renal transplantation at age 51	Diabetes, hypertension	No	114	49	0	No
12	71	M	s/p renal transplantation at age 67	Age	No	88	72	14	No
13	71	F	s/p renal transplantation at age 65	Age, obesity, hypertension, dyslipidemia	No	109	12	56	Yes
14	81	M	Nephrotic syndrome	Age, Hypertension, dyslipidemia	Age 79	88	19	38	Borderline

ECG: eceltrocardiography; fQRS: filtered QRS complex; RMS40: root-mean-square voltage of the terminal 40 ms; LAS: low-amplitude QRS signal; LP: late ventricular potentials
Note: The late potential test was considered abnormal when two of the following criteria were met: 1) fQRS > 114 ms; 2) RMS40 < 20 μV; and 3) LAS >38 ms

hypertension, and dyslipidemia). An echocardiogram demonstrated thickened interventricular septum (end-diastolic dimension of 14 mm), normal ejection fraction (55%), some wall motion abnormalities (inferobasilar and basilar-septum akinesis), abnormal diastolic relaxation, and moderate aortic stenosis. Notably, both the increased thickness of the interventricular septum and the presence of diastolic dysfunction could have resulted from cardiac amyloidosis, although they could have also stemmed from aortic valve stenosis. Myocardial biopsy was not performed. Five years prior to the study, he had undergone total thyroidectomy due to papillary carcinoma of the thyroid, and treatment with eltroxin had been initiated.

Discussion

In the present study of 54 FMF patients with and without AA amyloidosis, none had abnormal LPs except for 2 patients from the subgroup of 14 patients with FMF amyloidosis. These results reject our hypothesis that inflammation in FMF will result in a high rate of abnormal LPs. Thus, LP analysis infers lack of clinically significant cardiac involvement with atherosclerosis or amyloidosis in FMF.

To the best of our knowledge, our study is the first that analyzes LPs in FMF. Thus, we do not have the perspective of other centers' experience on this specific arrhythmogenic marker. Studies on other arrhythmogenic ventricular and supraventricular markers in FMF, which may shed light on our outcome, reveal conflicting results. Increased QTd, QTcd, QT variability index, and P-wave dispersion, suggesting higher propensity for arrhythmia in FMF, were reported by some authors but not by others (13, 20-23). Our experience looking at the same arrhythmogenic parameters is constantly similar, suggesting that uncomplicated FMF and even colchicine-resistant FMF are not associated with increased risk for cardiac arrhythmias (14, 24-26). These conflicting results may reflect a discrepancy between methodologies of data collection and processing, for example, computer-assisted methods used by us versus manual methods used by some other investigators or variations in genetic and environmental factors between the studied populations. Supporting our above data in uncomplicated and in colchicine-resistant FMF, however, is the finding of normal heart rate variability (HRV), which is another electrocardiographic marker with an overall and cardiac-related prognostic significance (27-29).

Even more surprising were the results in patients with amyloidosis, of whom 12 (~85%) had normal LPs. Even in the case of the two patients with abnormal LPs, one can argue that the abnormal LPs resulted from other cardiovascular noxious factors such as hypertension, dyslipidemia, old myocardial infarction, or aortic stenosis, all of which are known to be associated with abnormal LPs (30-32). This suggests that FMF amyloidosis, even after long duration (seven patients had already undergone kidney replacement therapy), may spare the heart and that inflammation in FMF, with a severe enough degree to cause systemic amyloidosis, may not

be sufficiently atherogenic to cause aberrant ventricular conduction. The negative results in the FMF amyloidosis group (who were subjected to the highest degree of adverse effects of inflammation) actually strengthen and validate our negative findings in uncomplicated FMF (the mildest stage in the spectrum of injurious effects of inflammation in FMF).

Our current findings in FMF-amyloidosis gain support from our previous studies assessing other arythmogenic markers. Those studies included a comparable population of FMF patients with amyloidosis who also showed normal results of QTd, QT variability, and P-wave dispersion (15, 33, 34). The LP results appear to disagree with the finding of low HRV parameters in FMF with progressive amyloidosis (35). However, the HRV finding may actually reflects the presence of autonomic dysfunction rather than cardiac AA amyloidosis. Thus, based on our current and previous results, it can be concluded that even in the progressive stage of FMF amyloidosis most electrophysiological arrhythmogenic markers are normal, thereby excluding increased risk for arrhythmia in this condition.

Studies assessing the actual prevalence of ischemic cardiovascular disease in FMF are scarce, but they indicate that it is normal and lower compared to that found in other inflammatory disorders (36). Colchicine, prescribed to all patients with FMF, has been suggested to be the cardioprotective factor that prevents the ill effects of inflammation (36-38). This cardioprotective effect of colchicine was shown to exist beyond the boundaries of FMF (37, 39). Thus, by failing to confirm that inflammation increases abnormal LPs and thereby the risk of arrhythmia in FMF, this study provides another example for the benefit gained by colchicine treatment in a population exposed to the deleterious effects of inflammation.

The shortcomings of the study include the relatively small group of amyloidosis patients. However, due to the current use of colchicine prophylaxis, FMF amyloidosis is rare, even in a very large FMF clinic such as ours encompassing more than 10,000 patients. Most of the patients were in a progressive state where involvement of cardiac amyloidosis is expected. Thus, despite the small group the results should be considered reliable. Another flaw is the absence of a control group of healthy individuals. However, the normal and abnormal standards of LPs are well established. The ECG criteria for abnormal LPs are universal and are not dependent on readings of certain control populations, similarly to the ECG definition of other cardiac disorders (left ventricular hypertrophy, first or second-degree AV block, etc.). Finally, the absence of myocardial biopsy is allegedly a major disadvantage in this study. However, ethical concerns regarding the lack of clinical or therapeutic benefits disqualify such a procedure. Moreover, in the absence of abnormal LPs, even academic reasoning to obtain tissue becomes very poor.

In conclusion, contrary to what might be expected in a major inflammatory disease, uncomplicated FMF patients have normal LPs. Thus, LP analysis joins previous electrocardiographic analyses that argue against an increased risk for reentrant ventricular arrhythmias, and perhaps against the occurrence of coronary atherogenesis, in FMF. In addition, no abnormal LPs were detected in most patients with FMF amyloidosis, indirectly lending support to the finding in uncomplicated FMF and suggesting that cardiac involvement in FMF amyloidosis is rare.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Sheba Medical Center.

Informed Consent: Written informed consent was obtained from who participated in this study.

Peer-review: Externally peer-reviewed.

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