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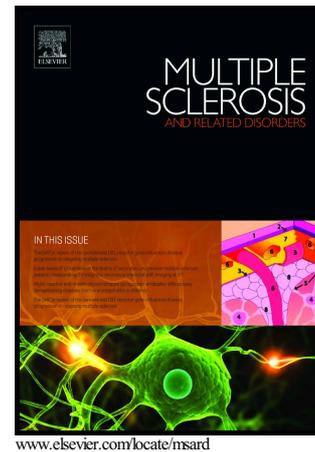
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Cardiac repolarization evolves differently during the course of benign and disabling multiple sclerosis

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Abstract

Background

Cardiac repolarization is modulated by the autonomic nervous system. Even though multiple sclerosis associates with prolonged cardiac repolarization the physiology responsible for the phenomenon remains unknown.

Objective

To study in longitudinal setting whether the patients with confirmed benign and disabling outcome of relapsing-remitting multiple sclerosis (RRMS) differ in regard to changes of cardiac repolarization.

Methods

Total of 43 patients, 26 % with benign (EDSS ≤ 2 at least 10 y after onset symptom) and 74 % with disabling (EDSS > 2 at least 10 y after onset symptom) RRMS, having 12-lead electrocardiogram (ECG) recorded at the time of onset symptom (ECG1) and for follow-up (ECG2), were studied. Heart rate (HR) corrected QT intervals (QTc) reflecting cardiac repolarization were assessed.

Results

The time interval between ECG1 and ECG2 showed no statistical difference between benign (7.8 ± 4.8 y) and disabling (10.2 ± 5.6 y; $p=0.211$) RRMS. Patients with benign and disabling RRMS showed similar values of HR (66 ± 9 bpm vs 73 ± 15 bpm; $p=0.146$) and QTc (403 ± 13 ms vs 408 ± 19 ms; $p=0.450$) at the time of ECG1. However, at the time of ECG2, HR was higher (79 ± 14 bpm vs 65 ± 10 bpm; $p=0.004$) and QTc was longer (420 ± 24 ms vs 400 ± 15 ms; $p=0.012$) in patients with disabling than benign RRMS. Correspondingly, HR increased ($p=0.063$) and QTc prolonged ($p=0.014$) during the disease course only in patients with disabling RRMS.

Conclusions

Deterioration of cardiac autonomic regulation during the disease course associates with disabling but not with benign RRMS. Our findings suggest that assessment of cardiac autonomic regulation should be included in the evaluation of RRMS disease course. In addition, patients with disabling RRMS might be prone to unfavorable cardiovascular outcome also due to deterioration of autonomic nervous system.

Keywords

Relapsing-remitting multiple sclerosis, RRMS, cardiac repolarization, QTc, heart rate, autonomic nervous system

1 Introduction

Relapsing-remitting multiple sclerosis (RRMS) is a chronic debilitating disease of the central nervous system. Disability is due to disease activity either in form of relapses with incomplete remissions, gradual progression of the disease, or both. The aim of RRMS treatment is to achieve and identify a disease state where no evidence of disease activity exists.¹

There is a subset of patients with benign RRMS who accumulate little or no disability during the disease course.^{2,3} Disability in RRMS is typically assessed by Expanded Disability Status Scale (EDSS), which relies heavily on ambulation. In the absence of changes in EDSS or brain magnetic resonance imaging lesion load over time, deterioration of cardiac autonomic function, however, may occur and reflect subclinical activity in MS.⁴ Autonomic dysfunction is commonly observed in patients with RRMS, and even in patients with clinically isolated syndrome.⁵

Autonomic nervous system and immune regulation are inherently linked.^{6,7} An anti-inflammatory reflex of the autonomic nervous system is conveyed via the parasympathetic vagus nerve. This cholinergic mechanism can inhibit cytokine release and is suggested to have a role in the prevention of tissue injury also in RRMS.⁸ In addition, parasympathetic and sympathetic branches of autonomic nervous system modulate cardiac repolarization,⁹ reflected by heart rate corrected QT (QTc) interval in the 12-lead electrocardiogram (ECG).¹⁰ Possible differences in the function of autonomic nervous system between patients with benign and disabling RRMS are, however, not known. The hypothesis of this study is that autonomic dysfunction evolves differently during benign and disabling course of RRMS.

In this study, we compared the function of autonomic nervous system by assessing heart rate and QTc interval from 12-lead ECG in the real-life patients with documented benign or disabling RRMS disease course.

2 Materials and Methods

We carried out an analysis of data collected from the patient records of Mikkeli Central Hospital and Kuopio University Hospital. All the patients with the diagnosis of MS were screened, but only those who subsequently developed clinically definitive RRMS (according to the McDonald 2010 criteria),¹¹ had at least 10 years follow-up from the onset symptom, and had ECG data available were included. 12-lead electrocardiogram (ECG) was recorded at the time of the symptom onset (ECG1), i.e the first demyelinating event causing clinical deterioration, in the neurology department before possible steroidal treatment. ECG2 was recorded during routine follow-up visit in non-acute phase. Patients with any disease influencing cardiac repolarization at the time of ECG1 or not in sinus rhythm were excluded (2 patients with hypertension, 1 patient with type 1 diabetes, one

patient with atrial fibrillation and 1 patient with ventricular bigeminy in ECG). The disease course was classified according to the EDSS score determined at a stable phase. Patients with EDSS score ≤ 2 after a minimum of ten years follow-up after the onset symptom were classified as benign³ RRMS group and patients with EDSS score >2 were classified as disabling RRMS group.

Kuopio University Hospital Research Ethics Committee approved the study protocol and the research was carried out in accordance with the Declaration of Helsinki (2008) of the World Medical Association. According to the recommendations of local ethics committee, the authorization for using a register data was obtained from the record controller.

2.1 Assessment of cardiac repolarization in electrocardiogram

The 12-lead ECGs were recorded in supine position. QT interval was assessed by automatic analysis and was defined as the interval from the onset of Q wave to the end of the T wave. All the analyses were manually confirmed. QT interval is influenced by heart rate and, therefore, needs to be adjusted accordingly for comparison. The heart rate corrected QT (QTc) interval was computed according to the Bazett formula $QTc_{Baz} = QT / \sqrt{RR - interval}$.

2.2 Statistical analysis

Kolmogorov-Smirnov test was applied to verify the normal distribution of the variables.

Comparisons of continuous variables were performed using the independent samples t-test and comparison of categorical variables using the Chi-square and Fisher's Exact test. The paired samples t-test was used for within group comparisons. All statistical analyses were performed using IBM SPSS Statistics for Macintosh (Version 22.0; Released 2013; Armonk, NY, USA). Results are

expressed as mean \pm standard deviation (SD), unless otherwise indicated. A P value ≤ 0.05 was considered statistically significant.

3 Results

3.1 Patients

Total of 43 patients were included in the study. The course of RRMS was found benign in 26 % (n=11) and disabling in 74 % (n=32) of patients. The patients with benign and disabling RRMS did not differ with respect to age, gender, systolic and diastolic blood pressure or IgG-index indicating the ratio between [cerebrospinal fluid immunoglobulin G vs albumin] and [serum immunoglobulin G vs albumin], at the time of ECG1 (Table 1).

The average time interval between ECG1 and ECG2 was 9.6 ± 5.5 y (range 1.1–22.0 y) and showed no statistical difference between the patients with benign (7.8 ± 4.8 y) and disabling (10.2 ± 5.6 y) RRMS (p=0.211).

None of the patients was on disease-modifying treatment (DMT) at the time of ECG1. At the time of ECG2, DMT was used by 67 % (29/43) of patients; 91 % (10/11) of patients with benign and 59 % (19/32) of patients with disabling RRMS, with no statistical difference between the groups (p=0.071). Specifically, at the time of ECG2, 14 patients were on interferon-beta, 9 patients were on glatirameracetate and 6 were on natalizumab. None of the patient were on oral DMT during the study, including fingolimod documented to have an effect on heart rate.¹² Concomitant medication

was found similar at the time of ECG1 and ECG2 in patients with benign and disabling RRMS (Table 2).

At the time of ECG1, the prevalence of concomitant diseases was found similar in patients with benign and disabling RRMS; asthma (9 % vs 9 %; $p=1.000$), rheumatoid arthritis (0 % vs 3 %; $p=1.000$), osteoporosis (0 % vs 3 %; $p=1.000$), depression (0 % vs 9 %; $p=0.558$) and schizophrenia (0 % vs 3 %; $p=1.000$) showed no statistical difference between patients with benign and disabling RRMS, respectively. Correspondingly, at the time of ECG2, the prevalence of concomitant diseases was also found also similar in patients with benign and disabling RRMS; diabetes (9 % vs 3 %; $p=0.451$), hypertension (9 % vs 9 %; $p=1.000$), coronary artery disease (9 % vs 0 %; $p=0.256$), asthma (9 % vs 13 %; $p=1.000$), rheumatoid arthritis (0 % vs 3 %; $p=1.000$), osteoporosis (0 % vs 3 %; $p=1.000$), depression (0 % vs 9 % $p=0.558$), bipolar disorder (0 % vs 3 %; $p=1.000$), schizophrenia (0 % vs 3 %; $p=1.000$), malignancy (0 % vs 3 %; $p=1.000$), epilepsy (0 % vs 6 %; $p=1.000$) and hypothyroidism (0 % vs 3 %; $p=1.000$) were similar in patients with benign and disabling RRMS, respectively.

3.2 Comparison of intervals in electrocardiogram between benign and disabling RRMS

At the time of ECG1, HR ($p=0.146$), QRS interval ($p=0.236$) QT interval ($p=0.296$) and QTc interval ($p=0.450$) were found similar in the patients with benign or disabling RRMS disease course (Table 3).

In ECG2, HR was higher in the patients with disabling than benign RRMS course ($p=0.004$). The patients with disabling RRMS showed a trend towards shorter QT interval in ECG2 compared to

the patients with benign RRMS ($p=0.064$). However, in ECG2, QTc was significantly longer in patients with disabling than benign RRMS ($p=0.012$) while QRS interval showed no difference between the groups ($p=0.494$) (Table 3).

3.3 Cardiac repolarization during the disease course

In the patients with benign RRMS, HR ($p=0.545$), QRS interval ($p=1.000$), QT interval ($p=0.826$) as well as QTc ($p=0.418$) were found substantially similar in ECG1 and ECG2 (Table 3). On the contrary, patients with disabling RRMS, had significantly longer QTc at the time of ECG2 than at the time of ECG1 ($p=0.014$) (Figure 1). In addition, HR tended to be higher in ECG2 than in ECG1 ($p=0.063$) in the patients with disabling RRMS. Uncorrected QT interval ($p=0.533$), as well as QRS interval ($p=0.318$), were similar between ECG1 and ECG2 in patients with disabling RRMS (Table 3).

The change in QTc interval between ECG1 and ECG2 was more pronounced in the patients with disabling than in the patients with benign RRMS as expressed in absolute ($p=0.021$) or in relative ($p=0.020$) units (Table 3).

A prolongation of QTc interval $>5\%$ during the follow-up was demonstrated in none (0%) of the patients with benign RRMS whereas it was true in 11 (34%) patients with disabling RRMS, with statistically significant difference between the groups ($p=0.041$). Accordingly, prolongation of QTc interval $<5\%$ during the follow-up predicted benign RRMS course with positive predictive value of 34%, negative predictive value of 100% and an accuracy of 51%.

4 Discussion

In this study, we demonstrated increase in heart rate and prolongation of cardiac repolarization (QTc interval) during the disease course in patients with disabling RRMS. In contrast, patients with documented benign disease course showed change neither in heart rate nor in cardiac repolarization.

At the time of the onset symptom, patients with disabling and benign disease course did not differ with respect to heart rate and cardiac repolarization. Accordingly, patients with disabling and benign RRMS disease course have similar characteristics of cardiac autonomic regulation assessed by heart rate and cardiac repolarization at the early disease course.

Cardiac repolarization showed significant prolongation during the years of disabling RRMS disease course. Correspondingly, at the later disease course, cardiac repolarization was found to be longer in the patients with a disabling than benign RRMS. In addition, heart rate had a trend to increase in the patients with accumulating disability during RRMS. To our knowledge, this is the first study to demonstrate that disabling and benign RRMS disease courses are distinct also in terms of its effect on cardiac autonomic regulation.

Patients with MS have demonstrated almost a threefold increase in mortality compared with general population.^{13,14} Although the reason for increased mortality is not fully understood, the higher-than-expected prevalence of infections has been reported in the death certificates of patients with MS.^{15,16} In addition, higher cardiovascular mortality has been suggested in patients with MS than in

general population.^{14,17} Previously, prolonged QT interval has been reported to associate with an increased risk of total, cardiovascular, and sudden cardiac death in general population,¹⁸ but no such data exists on RRMS patients. Autonomic nervous system has also an important role in the immune regulation via anti-inflammatory reflex.⁸ Accordingly, deterioration of the function of autonomic nervous system during the years of RRMS may have an unrecognized impact on the outcome of the RRMS patients.

EDSS quantifies disability in seven functional systems with an emphasis on motor domain but does not specifically take into account the integrity of autonomic nervous system. In our study, the disease course was classified as benign if the EDSS remained ≤ 2 at least 10 years after the first demyelinating event. This definition has recently been demonstrated to predict subsequent benign course also for another ten years,³ thus increasing the reliability of the definition. Previously, in the absence of the changes in EDSS or brain magnetic resonance T2 lesion load, cardiac autonomic function was suggested to reflect subclinical activity in MS during 2 years follow-up.⁴ In our study, patients with documented benign disease course did not show deterioration in heart rate or in cardiac repolarization over the seven-year period. This finding suggests that assessment of cardiac autonomic regulation should be included in the evaluation of RRMS disease course.

Disability in RRMS is considered to accumulate mainly due to neurodegeneration. Accordingly, brain^{19,20} and spinal cord^{21,22} atrophy have been associated with disability in RRMS patients. Previously, prolongation in QTc interval has also been found to associate with spinal cord atrophy secondary to axonal loss in MS patients.²³ In our study, longer cardiac repolarization was demonstrated at the later disease course in patients with disabling than benign RRMS. In view of

that, neurodegeneration in disabling RRMS may damage also the structures of central nervous system responsible for integration of autonomic functions.

Clinically assessed disability after long-term disease course is an obvious strength of our study. In addition, paired analysis of ECG recordings acquired at the early and later disease course of each RRMS patient gives an exceptional opportunity to assess longitudinal changes in cardiac autonomic function during real-life long-term disease course. Demographic parameters, use of disease modifying therapies, concomitant medication and accumulation of comorbidities were similar between the patients with disabling and benign RRMS and thus, may not confound our results. Possible steroidal treatments were given only after ECG1, and ECG2 was recorded in stable phase during routine follow-up visit and thus, steroidal treatment does not confound the results. On the other hand, the relatively small sample size is considered as a limitation of this study. In addition, retrospective setting and the lack of data about physical fitness or body constitution of the patients should be borne in mind while interpreting the results.

The duration of QT interval is influenced by heart rate and needs to be adjusted accordingly. Different correction formulae have been introduced but every method has specific flaws. As the Bazett formula has a tendency to over-correct QT interval at faster and under-correct at slower heart rates, the opposite bias is true for the Fridericia formula.¹⁰ At present, however, none of the heart rate correction methods for QT interval has been shown to be absolutely better than another. Due to mathematical properties, results based on different methods cannot be compared. In this study, the Bazzet formula was selected for correction as its features (flaws and benefits) are well established, method is commonly used and thus our results can be easily adapted to existing data.

5 Conclusions

Heart rate increases and cardiac repolarization prolongs during the course of disabling but not benign RRMS disease. These findings provide a broader understanding of the mechanisms leading to the deterioration of autonomic nervous system in patients with RRMS. Our results also suggest that benign RRMS does not have an effect on cardiac autonomic regulation and assessment of cardiac autonomic regulation should be included in the evaluation of RRMS disease course. In addition, patients with disabling RRMS disease might be prone to unfavorable cardiovascular and infective outcome due to deterioration of autonomic nervous system.

Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

Role of the Funding Source

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Figure 1. Heart rate corrected QT interval (QTc) in ECG1 (black bar) and in ECG2 (white bar) in patients with benign and disabling RRMS. Values are mean \pm SEM. Significance: ** $p = 0.014$.

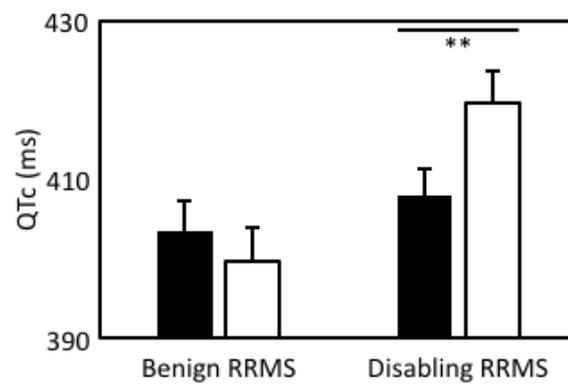


Table 1. Demographic data at the time of an electrocardiogram acquired at the early disease course in patients who demonstrated benign and disabling relapsing-remitting multiple sclerosis.

	Benign (n=11)	Disabling (n=32)	Significance
Age (years)	35±11	38±11	0.444
Female gender (%)	8 (73)	15 (47)	0.138
Li-Leuk ($\times 10^6/l$)	15.2±17.4	8.1±9.7	0.229
IgG-index	1.29±0.73	1.04±0.48	0.220
Na (mmol/l)	139±2	139±3	0.947
K (mmol/l)	4.1±0.4	4.0±0.3	0.534
sBP (mmHg)	136±23	134±17	0.863
dBP (mmHg)	81±11	81±13	0.901
Onset symptom			
Motor (%)	3 (27)	15 (47)	0.309
Vertigo (%)	0	1 (3)	1.000
Somatosensory (%)	5 (45)	7 (22)	0.241
Optic neuritis (%)	3 (27)	9 (28)	1.000

Values are mean \pm SD or number (%). Abbreviations: Li-Leuk = leukocyte concentration in cerebrospinal fluid, IgG-index = the ratio between [cerebrospinal fluid immunoglobulin G vs albumin] and [serum immunoglobulin G vs albumin], Na = plasma sodium concentration, K = plasma potassium concentration, sBP = systolic blood pressure, dBP = diastolic blood pressure.

Table 2. Medication at the time of an electrocardiogram acquired at the early (ECG1) and later (ECG2) disease course in patients with benign and disabling relapsing-remitting multiple sclerosis.

	<i>ECG1</i>			<i>ECG2</i>		
	Benign (n=11)	Disabling (n=32)	Significance	Benign (n=11)	Disabling (n=32)	Significance
Cardiovascular medication	0			2 (18)		0.156
ATII receptor blockers	0	0		1 (9)	1 (3)	1.000
β-blocking agents	0	0		0	3 (9)	1.000
Ca-channel blockers	0	0		1 (9)	1 (3)	0.256
Diuretics		0			0	
Nitrates		0			0	
Anti-cholinergics	2 (18)	2 (6)	0.267	3 (27)	5 (16)	0.401
Anti-depressants	2 (18)	6 (19)	1.000	3 (27)	13 (41)	0.494
Anti-epileptics	0	1 (3)	1.000	2 (18)	5 (16)	1.000
Anti-psychotics	0	1 (3)	1.000	0	2 (6)	1.000
Muscle relaxants	1 (9)	1 (3)	0.451	1 (9)	7 (22)	0.656

Values are number (%) of patients. Abbreviations: ACE = angiotensin converting enzyme, ATII = angiotensin II.

Table 3. Heart rate corrected QT intervals during disease course in patients with benign and disabling relapsing-remitting multiple sclerosis.

	Benign (n=11)	Disabling (n=32)	Significance
HR1 (bpm)	66±9	73±15	0.146
HR2 (bpm)	65±10	79±14	0.004
ΔHR (bpm)	-2±9	5±16	0.075
QRS1 (ms)	87±9	91±10	0.236
QRS2 (ms)	87±9	90±12	0.494
QT1 (ms)	385±23	373±34	0.296
QT2 (ms)	387±25	369±27	0.064
QTc1 (ms)	403±13	408±19	0.450
QTc2 (ms)	400±15	420±24	0.012
ΔQTc (ms)	-4±15	12±25	0.021
ΔQTc% (%)	-0.9±3.6	2.9±6.2	0.020

Values are mean ± SD. Abbreviations: HR = heart rate in ECG1 (1) and in ECG2 (2), QRS = QRS complex duration, QT = QT interval, QTc = heart rate corrected QT interval, Δ = absolute (ms) and relative (%) change between ECG1 and ECG2.

Highlights

- Traits of cardiac repolarization during benign and disabling RRMS remain unknown
- Cardiac repolarization prolongs in patients with disabling but not with benign RRMS
- Unaffected cardiac repolarization as a part of benign RRMS entity is suggested