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Research Article

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Increased Risk of Arrhythmias in Active Acromegaly with Complications and Persistent Uncontrolled Active Acromegaly

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Abstract

Objective: *Previous studies showed acromegaly have significant higher prevalence of ventricular arrhythmias and often complicated by diabetes mellitus (DM) and hypertension (HT). Both HT and DM are notoriously associated with the development of arrhythmias. However, the effect of complication (DM and/or HT) in acromegaly on ventricular arrhythmias and the risk of ventricular arrhythmias in acromegaly accept therapy but no control is largely unknown.*

Methods: *A cross-sectional study with 307 acromegaly and 303 patients with non-functional pituitary adenoma as control group. All subjects divided into acromegaly with/without complication and controls with/without complication. In the longitudinal study, 30 persistent uncontrolled active acromegaly with at least three months follow-up. Electrocardiographic Measurements, laboratory examination, and clinical data collection performed in all subjects. QT interval corrected for heart rate (QTc) analysed among groups.*

Results: *QTc in acromegaly population significantly increased compared to controls ($p<0.001$). Factorial design two-way ANOVA correcting age revealed significant main effects of complication ($p=0.016$) and acromegaly ($p<0.0001$), as well as positive interactions between complication and acromegaly ($P<0.038$) on QTc. Persistent uncontrolled active acromegalic patients after therapy showed QTc significantly increase in follow-up relative to pre-treatment ($p<0.0001$). The normalized GH level ($r=0.11$, $p<0.05$) and complication ($r=0.25$, $p<0.0001$) have a significant positive correlation with QTc in acromegaly.*

Conclusions: *Acromegaly is an independent risk factor for ventricular arrhythmias and acromegaly with complication have an elevated risk for ventricular arrhythmia. Persistent uncontrolled acromegaly, who have significantly decreased in serum GH/IGF-1 levels relative to pre-treatment, also enhance the risk of ventricular arrhythmia.*

Keywords: Active Acromegaly, Diabetes Mellitus (DM), Hypertension (HT), Ventricular Arrhythmias, Risk

1. Introduction

Acromegaly is a rare and chronic condition, mostly caused by pituitary adenoma, characterized by excess serum levels of growth hormone (GH) and insulin like growth factor-1 (IGF-1) [1,2]. Both GH and IGF-1 play a role in the physiology of cardiovascular system, excess serum GH and IGF-1 levels can result in major structural and functional changes in cardiac system, arrhythmias, and valvular heart disease [3,4]. Patients with acromegaly have significant mortality and reduction in life expectancy compare to healthy population, associated with cardiovascular, cerebrovascular disease and respiratory complications [5,6]. In these acromegalic patients, about 60% of patients die from cardiovascular disease [7,8]. Previous studies reported arrhythmias and/or conduction disorders have a high prevalence in acromegaly and ventricular arrhythmia may play an important role in fatal complication, such as sudden cardiac death [9,10]. Meanwhile, some studies also found multiple cardiovascular parameters can be improved during effective treatment of acromegaly [11,12]. However, some of acromegalic patients cannot achieve long-term biochemical control following surgical resection of the tumour and medical therapy, although achieving significant decrease of serum GH and IGF-1 levels [13].

The hypertension (HT) and diabetes mellitus (DM) are the common complications in acromegaly [14]. Both HT and DM have harmful effect on cardiac structure and function [15,16]. To date, however, whether the risk of arrhythmia increased in active acromegalic patient with complication (HT and/or DM) compare to active acromegalic patient without complication are largely unknown. Furthermore, to our knowledge, almost no follow-up studies have reported whether persistent uncontrolled active acromegalic patients, who have significantly decrease serum GH/IGF-1 levels after surgery and drug therapy, decrease the risk of ventricular arrhythmia. QT interval duration corrected for heart rate (QTc) at conventional electrocardiography (ECG) has long been recognized as a marker for predict serious ventricular arrhythmias and sudden cardiac death [17,18]. In the past decades, some studies demonstrated prolongation of QTc in acromegaly relative to healthy subjects and treatment of these patients is able to improve and even normalize this alteration [12,19].

In the current study, 307 patients with active acromegaly and 303 patients with non-functional pituitary adenoma as control group were recruited to study whether active acromegalic patient with complication (HT and/or DM) prolong QTc compare to active acromegalic patient with no complication. In addition, 30 uncontrolled active acromegalic patients have at least three months follow-up after therapy were included.

2. Methods and Material

2.1. Study Population

In the retrospective cross-sectional study, 307 patients with active acromegaly (growth hormone-secreting pituitary adenoma) and 303 patients with non-functional pituitary adenoma as control group recruited. In acromegaly and control group, all subjects divided into patients with complication (HT and/or DM) and patients without complication. In the longitudinal study, 30 persistent uncontrolled active acromegaly with at least three months follow-up were included. In our study, persistent uncontrolled active acromegaly defined as the serum GH and IGF-1 levels still above the age-adjusted normal range in acromegalic patients who accept therapy including surgery and/or drug. All the subjects from department of neurosurgery, Beijing Tiantan hospital between 2012 and 2019. Clinical features including age, sex, course of disease, and medical history of HT and DM collected. In all cases, acromegaly had been diagnosed by the presence of relevant clinical signs, increased serum GH and IGF-I levels, and/or failure of serum GH to be suppressed below 1μg/l after a 75-g oral glucose load. Hypertension had been diagnosed with poorly controlled blood pressure (SBP≥140 mmHg; DBP≥90 mmHg). Patients with overnight fasting plasma glucose >6.99 mmol/L on two consecutive events were defined as diabetic. In all subjects, the exclusion criteria as follows: a history of Mobitz type 2 block, left and right bundle branch block, third degree atrioventricular block, chronic liver disease, chronic kidney disease, atrial fibrillation, hyperthyroidism, primary hypothyroidism, congenital heart disease, coronary artery disease, congestive heart failure, sick sinus syndrome, ventricular pre-excitation and those with a permanent pacemaker. The study was performed in accord with the declaration of Helsinki and approved by the Beijing Tiantan hospital ethics committee.

2.2. Electrocardiographic (ECG) Measurements

All the patients underwent conventional 12-lead ECG for once, except 31 persistent uncontrolled active acromegalic patients evaluated at baseline and post follow-up. All ECG were examined after 10-minute rest and assessed by an experienced specialist. QT interval was measured by calculating the distance from the beginning of QRS complex to the end of T wave or the nadir of the wave between T and U waves if U wave presence. QT interval duration corrected for heart rate (QTc) was established according to the Bazett's Formula ($QTc = QT/\sqrt{RR}$ sec). In addition, heart rate (HR) assessed.

2.3. Laboratory Examination

In all subjects, the serum GH level and IGF-1 levels in venous blood samples, which collected between 06:00 a.m. and 10:00 a.m. following 10–12 h of fasting, measured using the IMMULITE 2000 immunoassay system (Siemens). To correct the effect of age and sex, serum IGF-1 and GH levels calculated as follows: serum IGF-1 or GH value/95th percentile of the age- and sex-adjusted normal range [20].

2.4. Statistical Analysis

Statistical analysis performed in IBM SPSS Statistics software (version 25). Group differences in nominal variables tested with Fisher's exact test and in continuous variables assessed by unpaired t-test or factorial design two-way ANOVA correcting age. When significant interactions observed between complication and acromegaly, a multiple comparison test, i.e. Sidak test used to determine differences among the groups. Paired samples t-test applied into pre-treatment and post follow-up parameters of patients. The Pearson's correlation were applied to confirm the relationship between the clinical factors (continuous data) and QTc. Non-parametric correlations were performed through Spearman's rank correlation coefficient. In all analysis, a two-tailed $P < 0.05$ considered statistically significant.

3. Results

3.1. Clinical Data and ECG Parameters of Acromegalic Patients and Control Group

In our study, 307 acromegalic patients and 303 controls collected. Table 1 shows detail clinical data and ECG parameters in acromegaly group and control group. No significant difference in age and sex between acromegaly group and control group. Normalized GH levels, HR, and QTc in acromegaly group significantly increased compared to control group ($p< 0.05$). In additional, there was significantly more subjects with complication in acromegaly than subjects with complication in control group ($p = 0.02$).

Characteristic	Acromegaly	Controls	P-value
Numbers	307	303	NA
Age (mean ± SD, years)	40.5 ± 10.3	41.8 ± 10.0	0.09[a]
Sex (M/F)	144/163	160/143	0.15[b]
Normalized serum GH	3.8 ± 3.9	0.1 ± 0.1	< 0.0001[a]
Normalized serum IGF-1	2.6 ± 0.9	NA	NA
Complication with HT and/or DM (n, % of total)	87 (28.3%)	62 (20.5%)	0.02[b]
HR	76.8 ± 11.5	72.1 ± 11.3	< 0.0001[a]
QTc (ms)	411.4 ± 17.6	405.4 ± 18.3	< 0.0001[a]

[a]Unpaired t-test, two-sided; [b]Fisher's exact test, two-sided.
Abbreviations: QTc: Frequency Corrected QT interval, HR: Heart Rate

Table 1: Demographic, Clinical Characteristics, and ECG Parameters between Acromegaly and Controls

3.2. The Effect of Acromegaly and Complication on QTc in Subjects

The detail clinical data and ECG parameters among active acromegaly with complication, active acromegaly without complication, controls with complication, and controls without complication summarized in Table 2. A factorial design two-way ANOVA correcting age revealed significant main effects of complication ($p = 0.016$) and acromegaly ($p < 0.0001$) on QTc Table 3. In additional, there were also significant interactions between complication and acromegaly ($P<0.038$, Table 3). As shown in Figure 1, acromegaly with complication showed higher QTc than acromegaly without complication ($p < 0.0001$) and controls with complication ($p < 0.0001$). Our result also showed QTc significantly increased in acromegaly without complication compared with controls without complication ($p = 0.027$, Figure 1).

Characteristic	Acromegaly (No complication)	Acromegaly (Complication)	Acromegaly (Complication)	Controls (Complication)
Numbers	220	87	241	62
Age (mean ± SD, years)	38.1 ± 9.6	46.1 ± 9.7	39.8 ± 9.6	49.5 ± 7.3
Sex (M/F)	98/122	46/41	122/119	38/24
Normalized serum GH	3.7 ± 3.8	4.1 ± 4.0	0.1 ± 0.1	0.08 ± 0.1
Normalized serum IGF-1	2.6 ± 0.9	2.9 ± 0.9	NA	NA
HR	76.79 ± 11.6	76.79 ± 11.3	71.3 ± 10.9	75.3 ± 12.3
QTc (ms)	408.5 ± 16.0	418.0 ± 19.6	404.8 ± 18.8	407.7 ± 16.1

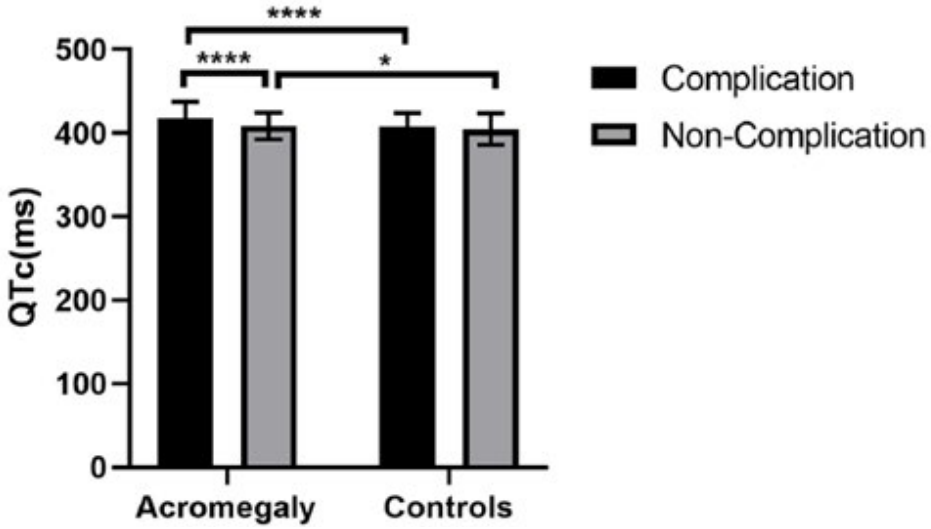
[a]Unpaired t-test, two-sided; [b]Fisher's exact test, [c]one-way ANCOVA correcting age, two-sided. Abbreviations: QTc: Frequency Corrected QT interval, HR: Heart Rate

Table 2: Demographic, Clinical Characteristics and ECG Parameters among Acromegaly With/Without Complication and Controls With/Without Complication

Characteristic	QTc			
	Sum Square	**df**	**F**	**P**
Age	2236.089	1	7.201	0.007
Complication	1820.304	1	5.862	0.016
Acromegaly	6149.485	1	19.803	0.000
Complication * acromegaly	1338.209	1	4.309	0.038
Total	201252.820	609	-	-

Abbreviations: QTc: Frequency Corrected QT interval

Table 3: Two-Way ANOVAs of QTc Correcting Age among Acromegaly With/Without Complication and Controls With/Without Complication



Data are mean ± SD. * represent $p < 0.05$, **** represent $p < 0.0001$ (ANOVA followed by a post hoc Sidak test).

Figure 1: The Effect of Acromegaly and Complication (HT and/or DM) on QTc

3.3. The Alteration of QTC in Patients with Persistent Uncontrolled Active Acromegaly

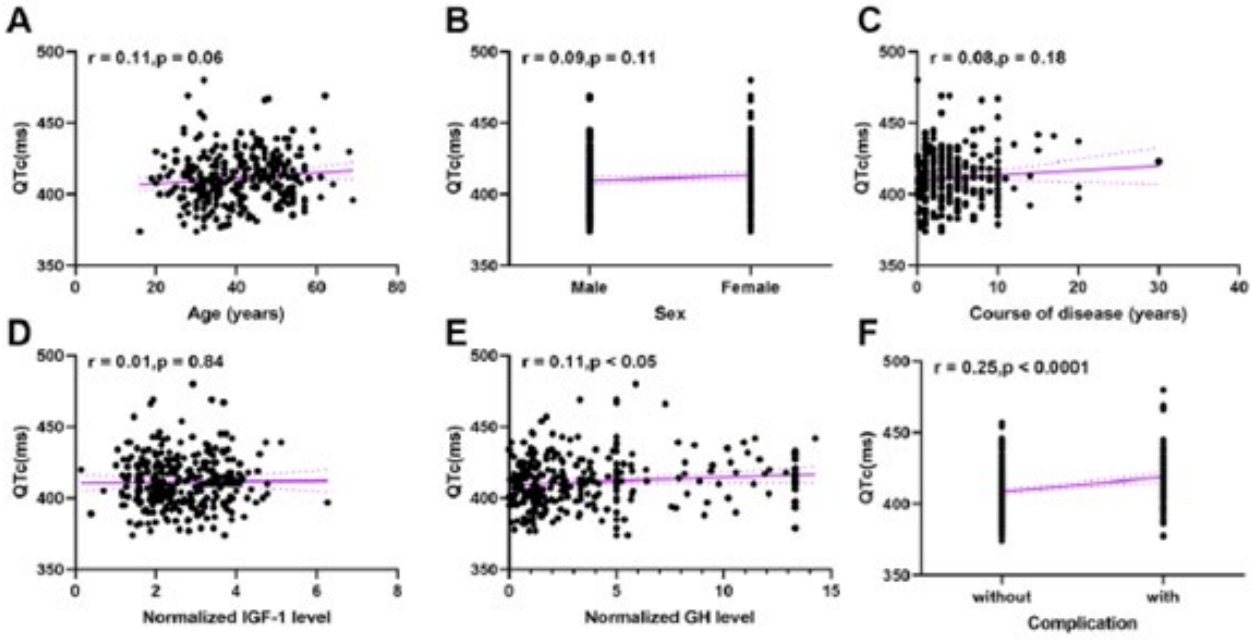
In persistent uncontrolled active acromegalic patients after surgery and drug therapy, the clinical features in baseline and post follow-up displayed in Table 4. In these uncontrolled active acromegalic patients, the results showed serum GH ($p = 0.006$) and IGF-1 ($p = 0.01$) levels significantly decrease compared with pre-treatment, but not up to cure standard. Dramatically, persistent uncontrolled active acromegalic patients showed QTc significantly increase in follow-up relative to pre-treatment ($p < 0.0001$, Table 4).

Characteristic	Pre-treatment	Follow-up	P-value
Age (mean ± SD, years)	37.1 ± 11.6	39.5 ± 11.5	< 0.0001a
Sex (M/F)	12/18	12/18	NA
Normalized serum GH	4.0 ± 3.7	2.5 ± 3.0	= 0.006a
Normalized serum IGF-1	2.6 ± 0.9	2.2 ± 0.9	= 0.01a
Follow-up interval (mean ± SD, months)	NA	28.4 ± 22.9	NA
QTc (ms)	398.8 ± 15.2	410.4 ± 14.6	< 0.0001a
[a]Paired t-test, two-sided, two-sided. **Abbreviations:** QTc: Frequency Corrected QT Interval			

Table 4: Demographic, Clinical Characteristics, and ECG Parameters in Active Acromegalic Patients with Follow-Up (n = 30)

3.4. Correlation Analysis Between Clinical Features and QTc in Acromegaly

In acromegaly, as shown in Figure 1, there are no significant relationship between QTc and age ($r = 0.11$, $p = 0.06$, Figure 2), sex ($r = 0.09$, $p = 0.11$, Figure 2), course of disease ($r = 0.08$, $p = 0.18$, Figure 2), and normalized IGF-1 level ($r = 0.01$, $p = 0.84$, Figure 2). The normalized GH level have a significant positive correlation with QTc in acromegaly ($r = 0.11$, $p < 0.05$, Figure 2). In addition, we also found a significant relationship between higher QTc and acromegalic patients with HT and/or DM ($r = 0.25$, $p < 0.0001$, Figure 2).



Relationship between QTc and age (A), sex (B), course of disease (C), normalized IGF-1 level (D), normalized GH level (E), and acromegalic patients with complication (F).

Figure 2: Correlation Analysis between Clinical Features and QTc in Acromegaly

4. Discussion

To the best of our knowledge, this is the first study to report the effects of acromegaly, complication (HT and/or DM), as well as persistent uncontrolled active acromegaly after therapy on QT interval. Our results showed that both acromegaly and complication prolonged QT interval in subjects. More importantly, we found that there is positive interaction between acromegaly and complication, which means acromegaly with complication significant prolong QT interval compared with subjects with acromegaly and subjects with complication. In addition, QT interval in persistent uncontrolled active acromegaly at follow-up was significantly longer than the value at pre-treatment. Serum GH level and complication (HT and/or DM) have a significant positive relationship with prolonged QT interval.

In acromegaly, long-term persistent excess serum GH/IGF-1 contribute to cardiac overgrowth, resulting in arrhythmias and/or conduction disorders [3]. In the past decades, previous studies have suggested prevalence and the severity of ventricular arrhythmias were significantly higher compared with controls by electrocardiogram and Holter studies in acromegaly [21,22]. For example, complex ventricular arrhythmias detected in 48% of acromegalic patients compared with only 12% of controls with 24-h Holter ECG [21]. Ventricular arrhythmias are clinically relevant, as it not only affects quality of life but also life threatening. QT intervals, reflecting the duration of ventricular repolarization, is an important period for the development of ventricular arrhythmias. QTc, correcting heart rate in QT intervals, has long been recognized as a marker of increased cardiovascular risk and provide important prognostic information in clinical practice [23]. Only a few studies investigated the alteration of QTc in acromegaly and found prolonged QTc compare with healthy population with a relatively small sample size [12,19,24]. In our study, 307 acromegalic patients and 303 patients with non-functional pituitary adenoma were included to study the difference of QTc between two groups. As consistent with previous studies, our result further demonstrated that prolonged QT interval in acromegaly population compare with controls by large sample data.

In acromegaly, long-term persistent excess serum GH/IGF-1 contribute to overgrowth of interstitial fibrous tissue within the myocardium is thought to be the predominant factor responsible for cardiac rhythm abnormalities [12,25,26]. It is well known that both HT and DM are frequent complication at the time of first diagnosis in acromegaly and HT and DM are notoriously associated with the development of arrhythmias. Maffei et al. detected heart rate variability reduced in acromegaly patients, especially with HT and/ or DM, compare to healthy populations [27]. To avoid the effect of DM and HT on QT intervals, CAKIR et al. recruit the control group from individuals with similar comorbidities (DM, HT) to the acromegalic patients [19]. In our study, all subjects were divided into four groups (acromegaly with complication, acromegaly without complication, controls with complication, and controls without complication) to investigate the effect of acromegaly and complication on QTc using factorial design two-way ANOVA. We found both acromegaly and complication significantly prolong QTc. Our results suggesting that both acromegaly and complication is an independent risk factor for ventricular arrhythmias. Notedly, we found that acromegalic patients with complication have significantly higher QTc than acromegalic patients without complication and controls with complication. This result suggested acromegalic patients with complication have a higher risk for ventricular arrhythmias.

Surgery, drug therapy, and radiotherapy are commonly used strategy in acromegalic patients to control serum GH/IGF-1 levels [13]. Fatti et al have reported QTc significantly reduced in acromegalic patients with primary somatostatin analogues therapy [12]. Recently, acromegalic patients with surgery was also found have statistically significant improvement QTc [19]. These studies suggested effective therapy could decrease the risk of ventricular arrhythmias in acromegaly. It has been already known that long-term persistent serum excess GH/IGF-1 is one of the main factors of cardiac dysfunction in acromegaly [28-30]. In our study, persistent uncontrolled active acromegalic patients after surgery and drug therapy were included. In these uncontrolled active acromegalic patients, serum GH and IGF-1 levels significantly decrease relative to pre-treatment, but not up to cure standard. Compare to pre-treatment, we found persistent uncontrolled serum excess GH/IGF-1 significantly increase the QTc. This result suggested the serum GH/IGF-1 levels in acromegaly patients should be strictly controlled significantly reduce of serum GH/IGF-1 levels but not reach the normal level after therapy cannot decrease the risk of ventricular arrhythmia.

In patients with acromegaly, serum GH and IGF-1 levels, age, course of disease, complication with hypertension and/or diabetes, and cardiovascular disease are the main determinants of mortality [31,32]. In the current study, we assess association of QTc with these clinical and echocardiographic variables. Previous studies have reported no relationship between GH/IGF-1 levels and QTc [12,19,24]. However, we found significant positive relationship between GH level and QTc. No associate was detected in previous studies may be due to relatively small sample size in their research. More importantly, we also found complication with HT and/or DM are markedly related to QTc. This finding further suggested acromegalic patients with HT and/or DM have higher risk for ventricular arrhythmia than acromegalic patients without HT and/or DM. As for course of disease, similar to previous studies, no significant relationship with QTc was found in the present study [12,19]. There are some reasons including most patients could not provide the time at which the symptoms began because the discovery of the disease was due to change in appearance, systemic comorbidities or to local tumor effects [33]. In addition, the time from tumorigenesis to the onset of symptoms does not provide an accurately assess the effect of on ventricular repolarization because different tumors secrete different hormones at different levels and individuals exhibit differences in hormone sensitivity.

5. Conclusions

In the current study, our results suggested that acromegaly is an independent risk factor for ventricular arrhythmias as well as active acromegalic patients with HT and/or DM have an elevated risk for ventricular arrhythmia. In addition, we found persistent uncontrolled active acromegalic, who have significantly decrease in serum GH/IGF-1 levels at post-treatment relative to pre-treatment, also enhance the risk of ventricular arrhythmia.

Ethics Approval and Consent to Participate

The Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (Beijing, China), approved the present study.

Availability of Data and Materials

The authors can confirm that all relevant data and materials are available upon request from the authors.

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Author Contributions

Design and conceptualized study: Yazhuo Zhang
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Analysed the data: Qiuyue Fang and Yulou Liu
Drafted the manuscript for intellectual content: Qiuyue Fang and Yazhuo Zhang

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