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ALTERNATION OF THE QRS COMPLEX - NEW OR WELL-FORGOTTEN OLD? CLINICAL OBSERVATIONS

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Three cases of registration of a rare electrocardiographic (ECG) phenomenon - alternation of the QRS complex (AQRS) are presented. AQRS was detected in two girls aged 6 and 16 with third variant of long QT syndrome (LQT3) and in an asymptomatic patient aged 13 with a family history of sudden death at a young age. AQRS was recorded in combination with macroscopic alternans of the T wave during Holter monitoring and bicycle ergometry. A definition of AQRS is given and possible mechanisms and clinical significance of the detected ECG phenomenon are discussed.

Key words: QRS alternans; long QT syndrome; LQT3; sudden cardiac death; mechanical and electrical cardiac alternans; Holter monitoring; bicycle ergometry

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Risk stratification for the development of life-threatening cardiac arrhythmias is a mandatory component of the assessment of patients from high-risk groups and is often based on electrocardiographic (ECG) markers of myocardial electrical instability [1-4]. Visible, so-called macroscopic T-wave alternans (MTWA) represents one of these validated ECG markers across different patient populations [5-8]. MTWA, in turn, is part of the broader concept of cardiac alternans, which encompasses not only cyclical changes in the T wave but also alternation of other ECG components [9].

In the present report, we describe three cases of a rare form of cardiac alternans manifested as QRS complex alternans (QRSA) during sinus rhythm and discuss its potential mechanisms and clinical significance.

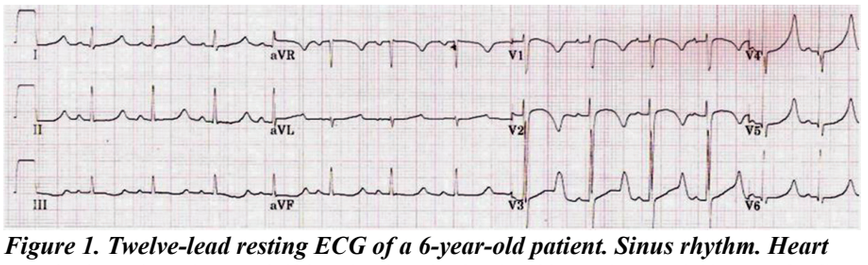

Figure 1. Twelve-lead resting ECG of a 6-year-old patient. Sinus rhythm. Heart rate 94 bpm (R-R interval 638 ms), electrical axis 68°, PR interval 134 ms, QRS duration 78 ms, QT interval 454 ms. Corrected QT interval calculated using Bazett's formula was 568 ms. T-wave (QT interval) morphology in lead II is characterized by a prolonged isoelectric ST segment.

Three patients (girls aged 6, 13, and 16 years) with ECG-documented QRSA identified between 2024 and 2025 were examined. All patients underwent comprehensive clinical and cardiological evaluation, including physical examination, detailed family history with emphasis on sudden cardiac death, complete blood count and urinalysis, biochemical blood tests with electrolyte assessment, resting 12-lead ECG, high-resolution ECG, transthoracic echocardiography (TTE), exercise testing (bicycle ergometry or treadmill test), and 24-hour Holter monitoring. To exclude Brugada syndrome, ECG recordings in high parasternal (precordial) leads were performed [10].

Patient 1

A 6-year-old girl. During a routine pre-school ECG screening, prolongation of the corrected QT interval (QTc) up to 568 ms was identified on a resting 12-lead ECG (Fig. 1). The QT interval configuration in lead II was characterized by a prolonged isoelectric ST segment and delayed onset of the T wave. No ventricular late potentials were recorded, and there were no ECG findings suggestive of Brugada syndrome.

The patient was asymptomatic, received no medical therapy, and had no history of syncope. The mother denied any family history of sudden cardiac death. Physical examination was unremarkable. TTE showed no abnormalities. Complete blood count, urinalysis, biochemical blood tests, serum electrolytes, and thyroid hormone levels were within normal limits. ECGs of both parents and two siblings showed no QT interval prolongation. Holter monitoring revealed no clinically significant arrhythmias.

Molecular genetic testing identified a de novo mutation in the SCN5A gene, classified as pathogenic (class V). A heterozygous variant NM_000335:c.1231G>A (p.Val411Met) was detected in exon 10 of the SCN5A gene and was considered potentially related to the observed phenotype. Pathogenicity classification was assigned in accordance with current recommendations [11].

A diagnosis of long QT syndrome (LQTS), molecular-genetic variant 3 (LQT3) was established. During nocturnal sleep, intermittent episodes of QRSA were recorded in combination with MTWA, manifested as beat-to-beat cyclical changes in QRS complex amplitude and T-wave morphology, without evidence of premature beats (Fig. 2).

Exercise testing (treadmill) revealed no rhythm disturbances, ischemic changes, or alternans phenomena. The patient's ECG findings had been previously described by us prior to molecular genetic testing and initiation of therapy [12,13].

Treatment with atenolol (1 mg/kg/day in two divided doses) was initiated, followed by the addition of flecainide (2 mg/kg/day in two divided doses). Given the identified genetic variant, persistence of QTc prolongation >500 ms despite therapy, and the presence of MTWA, implantation of an implantable cardioverter-defibrillator (ICD) was recommended.

Patient 2

A 16-year-old girl with a history of syncopal episodes and a family history of sudden cardiac death. Resting 12-lead ECG demonstrated QTc prolongation up to 522 ms (Fig. 3). The QT interval configuration in lead II was characterized by a prolonged isoelectric ST segment and delayed onset of the T wave. Structural heart disease, cardiomyopathies, inflammatory conditions, and electrolyte disturbances were excluded. The patient was not receiving any medical therapy.

No ventricular late potentials were recorded, and there were no ECG findings suggestive of Brugada syndrome. Molecular genetic testing revealed a known pathogenic mutation in the SCN5A gene (pathogenicity class V), identified both in the patient and her mother, in contrast to Patient 1. A heterozygous pathogenic variant NM_001099404.2:c.5350G>A (p.Glu1784Lys) was detected in exon 28 of the SCN5A gene and was considered potentially related to the observed phenotype. Pathogenicity classification was assigned in accordance with current recommendations [11].

A diagnosis of long QT syndrome (LQTS), molecular-genetic variant 3 (LQT3) was established. During 24-hour Holter monitoring, episodes of QRSA in combina-

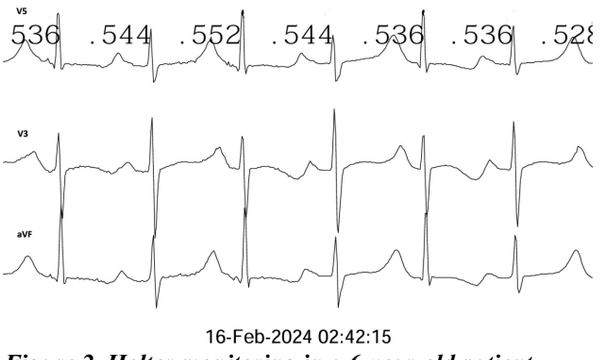

Figure 2. Holter monitoring in a 6-year-old patient. T-wave alternans (cyclical alternation of T-wave morphology) and QRS alternans (cyclical alternation of QRS complex amplitude from the second to the fifth beat) recorded in all leads during nocturnal sleep (03:54) in a patient with long QT syndrome (LQT3). R-R intervals (ms) are indicated in lead V5.

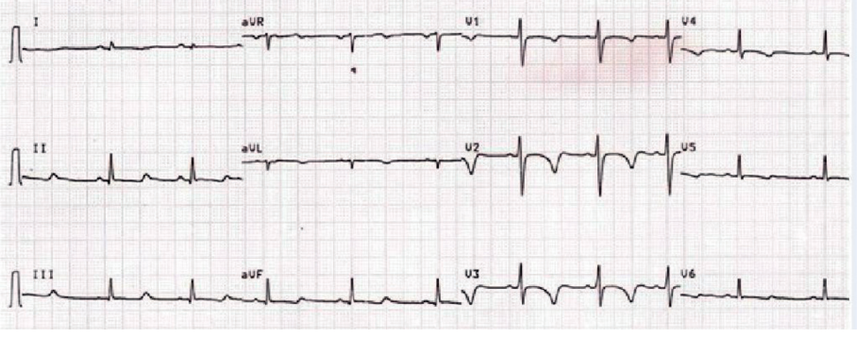

Figure 3. Resting 12-lead ECG of a 16-year-old patient with long QT syndrome (LQT3). Sinus rhythm. Heart rate 66 bpm, QTc = 522 ms. The QT interval demonstrates a prolonged ST segment with delayed onset of the T wave.

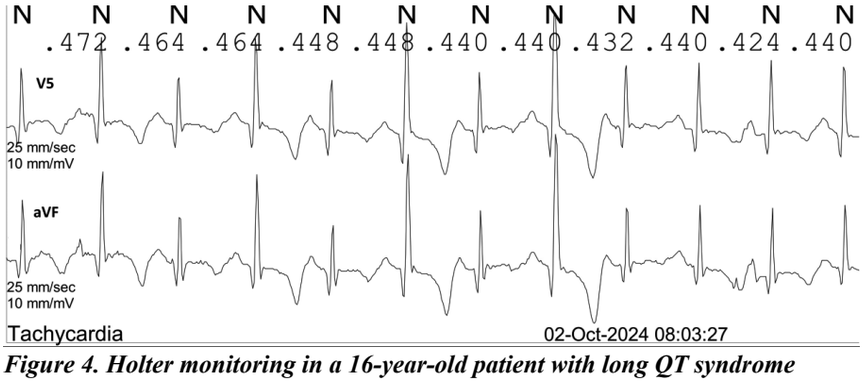

Figure 4. Holter monitoring in a 16-year-old patient with long QT syndrome (LQT3). Sinus rhythm, heart rate 134 bpm. QRS alternans (cyclical alternation of QRS complex amplitude) and T-wave alternans recorded in modified Holter leads V5 and V3. R-R intervals (ms) are shown in lead V5.

tion with MTWA were recorded in modified Holter leads (Fig. 4). Periods of QRSA and MTWA were observed both during nighttime and daytime hours.

During bicycle ergometry testing, no arrhythmias or ischemic changes were detected. However, at the first workload stage, within a heart rate range of 120-130 beats per minute, QRSA was observed in leads II, aVL, aVR, V1, V2, and V3, associated with MTWA (Fig. 5). The electrical axis of the heart measured 94° during non-alternating beats and 105° during alternating beats. QRSA resolved at heart rates exceeding 130 beats per minute.

Therapy with atenolol (1 mg/kg/day in two divided doses) was initiated, followed by the addition of flecainide (2 mg/kg/day in two divided doses). Given the identified genetic variant, persistence of QTc prolongation >500 ms despite therapy, presence of MTWA and a history of syncope, implantation of an ICD was recommended. The case had been previously reported by our group prior to initiation of therapy [14].

Patient 3

A 13-year-old girl, a competitive athlete (softball), was referred for evaluation after suspicion of a coronary artery anomaly was raised during routine periodic in-depth medical screening of athletes. TTE revealed features suggestive of a retroaortic anomalous coronary artery course (RAC sign). The patient was asymptomatic, denied syncope, and was not receiving any medical therapy.

Family history was notable for sudden death of a brother at the age of 18 years (cause undetermined) and death of the maternal grandfather at the age of 60 years (reported by the patient's mother as a "heart attack"). Physical examination was unremarkable. Complete blood count, urinalysis, biochemical blood tests, serum electrolytes, and thyroid hormone levels were within normal ranges. Ventricular late potentials were not detected, and there were no ECG findings suggestive of Brugada syndrome.

Resting ECG demonstrated a heart rate of 71 beats per minute with normal PR and QT intervals (QTc 435 ms). Holter monitoring did not reveal any pathological findings. According to multislice computed tomography of the heart and coronary angiography, the presence of right coronary artery hypoplasia could not be excluded. A small pericardial effusion was also noted. Stress myocardial perfusion scintigraphy did not demonstrate significant perfusion defects or stress-induced myocardial ischemia.

During bicycle ergometry testing, no arrhythmias or ischemic changes were recorded. However, at the first workload stage, within a heart rate range of 110-130 beats per minute, QRSA was observed in leads aVR and V1, associated with MTWA (Fig. 6). QRSA resolved at higher heart rate values. The electrical axis of the heart was 93° during non-alternating cycles and 87° during alternating cycles.

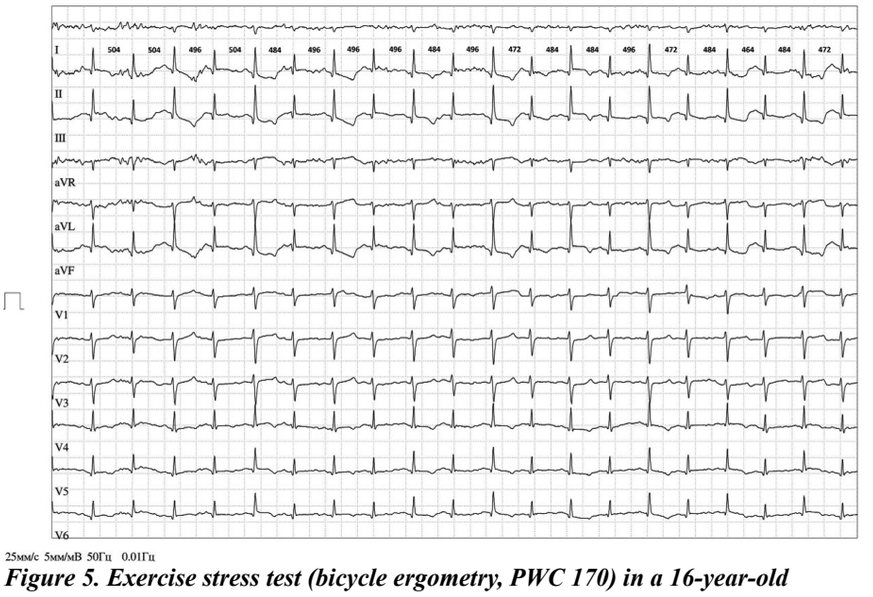

Figure 5. Exercise stress test (bicycle ergometry, PWC 170) in a 16-year-old patient with long QT syndrome (LQT3) at the first workload stage. Sinus rhythm. Heart rate 115 bpm. Combined QRS complex alternans and macroscopic T-wave alternans observed in leads II, III, aVR, aVL, aVF, V2, and V3. R-R intervals (ms) are indicated in lead II.

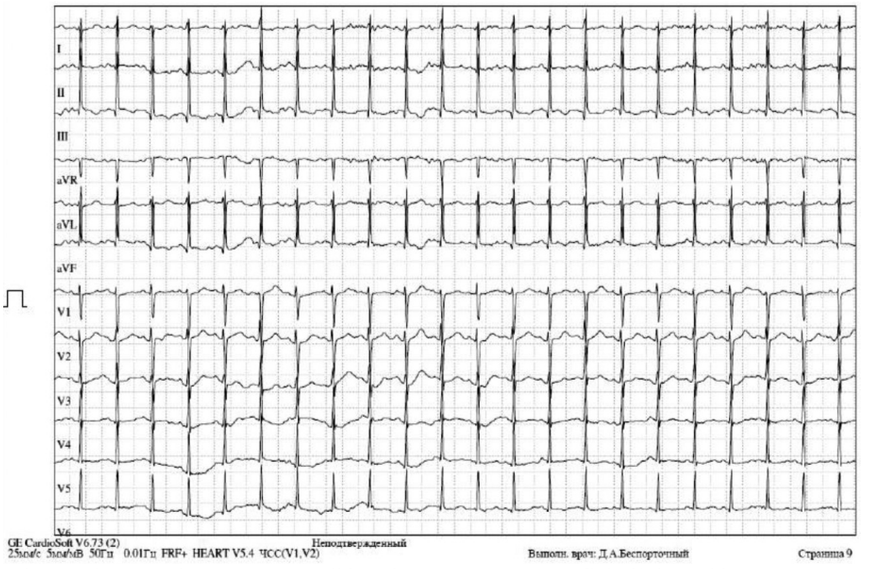

Figure 6. Exercise stress test (bicycle ergometry, PWC 170) in a 13-year-old patient at the first workload stage. Sinus rhythm. Heart rate 115 bpm. Combined QRS complex alternans and macroscopic T-wave alternans observed in leads aVR and V1.

Given the absence of symptoms, lack of confirmed pathological coronary artery anomalies, absence of myocardial ischemia, and absence of clinically significant arrhythmias, no treatment was initiated. Considering the family history, molecular genetic testing was recommended to exclude arrhythmogenic channelopathies and cardiomyopathies, in accordance with protocols for evaluation of family members in whom unexplained sudden death at a young age has been documented [15].

In all examined patients, RR interval variation during alternating cycles ranged from 8% to 13%, QRS complex width varied by no more than 10%, and the electrical axis of the heart during stress testing deviated rightward/downward by 10% in the 16-year-old patient (Patient 2) and leftward/upward by 6% in the 13-year-old patient (Patient 3).

Based on analysis of all recorded episodes of QRSA in the three patients, we propose the following definition of electrical QRS alternans on sinus rhythm:

Electrical QRS alternans on sinus rhythm is defined as a beat-to-beat cyclical change in QRS complex amplitude with minimal variation in QRS duration and RR intervals in alternating consecutive sinus cycles, lasting for at least six consecutive RR intervals and recorded in at least two ECG leads, by analogy with the definition of macroscopic T-wave alternans, in patients without cardiac diseases associated with pericardial effusion [5].

DISCUSSION

The study of cardiac alternans has a long history. As early as 1872, L. Traube published observations of beat-to-beat changes in pulse intensity (pulsus alternans) in a patient with cardiomyopathy and heart failure who died suddenly two months later [16]. In 1909, H. Hering documented QRSA and MTWA in animal experiments, while T. Lewis was the first to describe cardiac alternans in patients during psycho-emotional stress [17, 18]. In contemporary literature, QRSA is regarded as part of the broader concept of cardiac alternans [9].

B. Surawicz distinguished between mechanical and electrical QRSA [9]. Mechanical QRSA is associated with conditions accompanied by pericardial effusion, cardiac tamponade, and exudative pericarditis, in which the phenomenon of a “swinging heart” occurs. In such cases, the electrical axis of the heart changes from beat to beat due to cardiac motion within the pericardial fluid, and QRSA resolves after drainage of the effusion [19].

The mechanism of electrical QRSA is linked to delayed conduction or conduction block within the His-Purkinje system or ventricular myocardium, typically observed in patients with paroxysmal supraventricular or ventricular tachycardias [20]. In 1978, H. Klein et al. reported a case of QRSA on sinus rhythm caused by intermittent incomplete left anterior fascicular block occurring every second beat during procainamide therapy [21]. The authors concluded that when QRSA on sinus rhythm is not related to a large pericardial effusion, it should be classified as pseudo-electrical alternans. According to their interpretation, such alternans may result from cyclical changes in QRS amplitude due to alternating conduction within the His-Purkinje system without changes in the physical orientation of the heart, or may be related to ventricular bigeminy in which late premature beats are synchronized with normal QRS complexes, causing axis deviation every other beat.

A. Bayés de Luna described QRSA occurring in patients without cardiac tamponade or paroxysmal tachyarrhythmias as false alternans, often related to respiratory motion during ECG recording in precordial leads. This category includes observations reported by E. Schulze-Bahr, such as transient Wolff-Parkinson-White syndrome, bigeminy with long pre-ectopic intervals, and related phenomena [22-24].

There are, however, isolated reports of QRSA on sinus rhythm that do not fit these definitions, as they occur in the absence of pericardial effusion, drugs affecting intraventricular conduction, or conditions associated with so-called false alternans, and are not accompanied by overt arrhythmogenic events [21, 22, 25]. In such cases, the mechanism of QRSA remains hypothetical and its clinical significance uncertain. These atypical variants of QRSA were observed in our patients.

In the 6-year-old girl (Patient 1), QRSA was recorded during nighttime hours, corresponding to a period of maximal arrhythmogenic vulnerability in LQT3 [26]. In the patient with a more severe LQT3 phenotype (Patient 2), combined QRSA and MTWA were also observed during daytime hours and during exercise testing. MTWA is a well-established arrhythmogenic trigger in patients with long QT syndrome; therefore, the coexistence of QRSA and MTWA in these patients suggests that QRSA may represent a highly probable proarrhythmic marker of myocardial electrical instability [1, 5].

This hypothesis is supported by the experimental study by M. Chinushi et al., who demonstrated in a canine LQT3 model that periods of combined QRSA and MTWA arise due to delayed conduction in mid-myocardial layers (as opposed to epicardium or endocardium) and serve as precursors or triggers of torsade de pointes ventricular tachycardia, which developed even in the absence of a triggering ventricular premature beat [27].

In the 13-year-old patient (Patient 3), no overt cardiac disease was identified. A clinically significant coronary artery anomaly was not definitively confirmed, no ischemic changes were detected, known channelopathies were excluded, and the small pericardial effusion was insufficient to cause a “swinging heart” phenomenon and mechanical QRSA. Nevertheless, the adverse family history, including sudden death at a young age (brother aged 18 years), cannot be ignored and warrants further evaluation [15].

In the treatment of our two patients with long QT syndrome, standard beta-blocker therapy was employed, with the addition of the sodium channel blocker flecainide, a drug approved in the Russian Federation that shortens the QT interval specifically in patients with the LQT3 molecular-genetic subtype [28, 29].

CONCLUSION

At present, accurate risk stratification in patients with QRS complex alternans on sinus rhythm in the absence of pericardial effusion remains unclear. It is highly likely that the electrophysiological mechanisms underlying this ECG phenomenon increase the risk of cardiac events in patients with an arrhythmogenic myocardial substrate (including

channelopathies, cardiomyopathies, and myocardial ischemia). This uncertainty underscores the need for long-term follow-up and further accumulation of clinical and electrophysiological data.

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