Cardiac work up in primary renal hypokalaemia-hypomagnesaemia (Gitelman syndrome)

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Abstract
Background. Potassium and magnesium depletion prolongs the duration of the action potential of the cardiomyocyte, which predisposes to ventricular arrhythmias. In addition, potassium or magnesium depletion might impair cardiac performance and facilitate coronary artery thrombosis.

Methods. Continuous 24-h ambulatory electrocardiographic monitoring, treadmill exercise testing and echocardiography were assessed in 21 patients (11 female and 10 male subjects, aged 5.9–39, median 19 years) with primary renal hypokalaemia-hypomagnesaemia.

Results. The QT interval corrected for heart rate was normal (between 379 and 430 ms) in 10 and slightly to moderately prolonged in the remaining 11 patients (between 446 and 509 ms). Plasma potassium, magnesium and bicarbonate were similar in patients with normal and in those with prolonged QT interval. Continuous ambulatory electrocardiography over 24 h and exercise testing did not detect significant abnormalities of cardiac rhythm or features suggestive of myocardial ischaemia. Finally, echocardiographic and Doppler assessment failed to reveal any abnormalities in myocardial morphology and function.

Conclusion. The QT interval is often prolonged in primary renal hypokalaemia-hypomagnesaemia, confirming that potassium and magnesium depletion tends to prolong the duration of the action potential of the cardiomyocyte. The results of continuous ambulatory electrocardiography, exercise testing and echocardiography are reassuring. Nonetheless, we assume that dangerous cardiac arrhythmias may occur in patients with very severe hypokalaemia, during medication with drugs that prolong the QT interval or in the context of short-term non-adherence to the recommended regimen of care.

Keywords: echocardiography; exercise testing; Gitelman syndrome; Holter monitoring; QT interval

Introduction
Primary renal hypokalaemia-hypomagnesaemia [1], mostly reported as Gitelman syndrome (Mendelian Inheritance in Man # 263800) is an autosomal recessive renal disorder mostly caused by inactivating mutations in the gene coding for the thiazide-sensitive sodium chloride co-transporter in the distal convoluted tubule. The disease is characterized by hypokalaemia, hypomagnesaemia, alkalosis and rather low urinary calcium excretion rates [2–5].

Potassium or magnesium depletion prolongs the duration of the action potential of the cardiomyocytes and consequently increases the QT interval on electrocardiogram (ECG), which imparts an increased risk for development of ventricular arrhythmias culminating in syncope or sudden death [6,7]. Accordingly, recent observations indicate that the QT interval on standard ECG is often prolonged in Gitelman syndrome [8]. In addition, potassium or magnesium depletion might impair cardiac performance and facilitate coronary artery thrombosis [7,9].

Considering the derangements of the cardiovascular system that have been associated with potassium and magnesium deficiency, continuous 24-h ambulatory electrocardiographic monitoring, treadmill exercise testing and echocardiography were assessed in a rather large group of patients with Gitelman syndrome.
Subjects and methods

Twenty-five Italian (n = 23) or Swiss (n = 2) patients (13 female and 12 male subjects, aged 5.9–39, median 18 years) from 20 kindreds with Gitelman syndrome were enrolled in the study. The patients were clinically well characterized through long-term follow up and inclusion in previous studies [8,10–13]. Mutations in the thiazide-sensitive sodium chloride co-transporter gene had been identified in 17 patients by single-stranded conformation polymorphism, using polymerase chain reaction primers designed from intronic sequences surrounding all 26 exons of the gene, as described previously, whereas the remaining eight patients were genetically not characterized at the time of the study [13]. The patients did not discontinue long-term supplementation with potassium (n = 16) or magnesium (n = 21) or medication with non-selective cyclooxygenase inhibitors (n = 3). However, none of the Gitelman patients used drugs that have been associated with cardiac arrhythmias, including anti-arrhythmic agents, anti-histamines, macrolides, anti-fungals, psychotropics, β2-adrenergic agonists or cisapride [6]. None of the patients had a history of unexplained loss of consciousness with postural collapse, non-febrile seizures, chest discomfort, palpitations and exertional or nocturnal shortness of breath. In addition, a meticulous clinical examination failed to reveal any cardiovascular abnormality.

The patients were instructed to collect urine during 24 h for determination of creatinine and to attend the outpatient clinic after overnight fasting. Body weight and height were measured, and a blood sample collected with minimal stasis and without movements of the forearm for the determination of plasma potassium, total magnesium, bicarbonate, creatinine, total calcium, sodium and inorganic phosphate using standard laboratory techniques [11,12]. The values noted in Gitelman patients were compared with previously reported reference values [11,12].

In the patients, a standard 12-lead resting ECG, a 24-h ambulatory electrocardiographic monitoring, a treadmill exercise testing and an echocardiography were recorded.

The QT interval was assessed at a paper speed of 50 mm/s and an amplification of 0.1 mV/mm on lead II. The QT interval was measured from the earliest onset of the QRS complex to the latest point at which the T wave crosses the baseline (U waves were not measured as part of the QT interval). The QT interval and the preceding RR interval were measured for five consecutive cycles and averaged. The QT interval corrected for heart rate was calculated from the measured QT interval and from heart rate (RR interval) using the Bazett formula. The normal value for the corrected QT interval is < 440 ms [6,8].

Continuous ambulatory electrocardiography over 24 h was recorded and subsequently evaluated for (i) rhythm and conduction abnormalities; (ii) the minimum, average and maximum heart rate; (iii) the frequency of premature atrial, junctional or ventricular arrhythmias; and (iv) ischaemic episodes. Rhythm abnormalities were defined as the presence of at least one of the following: atrioventricular heart block, atrial flutter or fibrillation, and supraventricular or ventricular tachycardia. The 24-h electrocardiography was judged to be normal if there were no rhythm or conduction abnormalities, episodes of bradycardia or tachycardia or ischaemia. Thirty or less ventricular premature complexes per hour were considered as normal [14].

Exercise testing was performed using the modified Bruce walking treadmill protocol to voluntary exhaustion with simultaneous continuous electrocardiographic monitoring [15,16]. The electrocardiographic features were analysed with respect to significant ST-segment changes indicative of ischaemia, increasing complex ectopy or ventricular tachycardia. Five or less ventricular premature complexes were considered as normal [14].

Two-dimensional, M-mode and Doppler echocardiography was performed with an Acuson XP 800 recorder. Measurements included the left atrial dimension, the left ventricular internal dimension at end-diastole, the interventricular septum wall thickness at end-diastole, the posterior left ventricular wall thickness at end-diastole and the left ventricular mass (that were indexed for body surface area), the fractional shortening, a parameter of left ventricular systolic function, and the E/A ratio, a parameter of left ventricular diastolic function. The values noted in the patients were compared with those obtained in healthy Italian subjects using an identical apparatus.

The results of continuous variables are given as median, interquartile range (which extends from the value at centile 25 to that at centile 75 and includes half of the data points) and ranges. The two-tailed Kruskal–Wallis test (non-parametric analysis of variance for independent samples) with the Bonferroni adjustment and simple regressions with the non-parametric coefficient of determination r² were used for analysis. Significance was assumed when P < 0.05.

Results

Biochemical data

In the 25 patients with Gitelman syndrome a tendency towards hypokalaemia (plasma potassium ranging between 2.6 and 3.7 mmol/l; reference 3.5–5.0 mmol/l or more), hypomagnesaemia (plasma magnesium from 0.50 to 0.75 mmol/l; reference 0.72–0.94 mmol/l) and interfascicular septal wall thickness between 2.6 and 3.7 mmol/l; reference 22.1–28.2 mmol/l) was noted. The creatinine clearance [from 86 to 12] ml/(min 1.73 m²); reference 80–130 ml/(min 1.73 m²)].

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It was normal (between 379 and 430 ms) in 10 and slightly to moderately prolonged in the remaining 11 patients (between 446 and 509 ms). Plasma potassium, magnesium and bicarbonate were not statistically different in patients with normal and in patients with prolonged QT interval corrected for heart rate.

**Holter monitoring**

Continuous ambulatory electrocardiography over 24 h failed to detect rhythm or conduction abnormalities and episodes of bradycardia or tachycardia both in 10 patients with normal as well as in 11 patients with prolonged QT interval corrected for heart rate on standard 12-lead resting ECG. Furthermore, continuous ambulatory electrocardiography failed to detect episodes of ischaemia.

**Treadmill exercise testing**

All patients achieved predicted maximum heart rate for age. The 21 patients were in sinus rhythm at rest, during and after exercise. Furthermore, no ST-T changes were observed on the ECG during exercise or during the immediate recovery period.

**Echocardiographic and Doppler findings**

The echocardiographic and Doppler features noted in the Gitelman patients are given in Table 1. Left atrial dimension, left ventricular internal dimension at end-diastole, interventricular septum wall thickness at end-diastole, posterior left ventricular wall thickness at end-diastole, left ventricular mass, the fractional shortening and the E/A ratio were normal in the patients.

**Discussion**

Potassium and magnesium depletion can result in some cardiovascular derangements [6,7,9]. The present study represents the first systemic cardiac work up in a rather large group of children and young adults with Gitelman syndrome. The results confirm recent data indicating that the QT interval on standard ECG is often mildly to moderately prolonged in this disease condition. However, continuous ambulatory electrocardiography over 24 h and exercise testing did not detect significant abnormalities of cardiac rhythm. Finally, echocardiographic and Doppler assessment failed to reveal any abnormalities in myocardial morphology and function.

The present study confirms the potential of potassium or magnesium depletion to alter ventricular repolarization, as indicated by the fact that in Gitelman syndrome the QT interval on standard ECG was often prolonged [8]. On the other side, the similar plasma potassium, magnesium and bicarbonate levels in patients with normal and in those with prolonged QT interval suggest that the altered ventricular repolarization is more linked to their concentration gradient across the cardiomyocytic membrane than to their extracellular level.

In the present study, continuous ambulatory electrocardiography and exercise testing failed to detect significant abnormalities of cardiac rhythm in Gitelman patients. A similar tendency towards long QT interval but without abnormalities of cardiac rhythm during Holter recording has been reported previously in a small and rather heterogeneous group of patients with renal hypokalaemia [17]. The results of continuous ambulatory electrocardiography and exercise testing obtained in this study are reassuring, supporting the recent suggestion that clinically relevant arrhythmias do not occur in patients with normotensive hypokalaemic tubulopathies [18]. Nonetheless, we assume that dangerous cardiac arrhythmias may occur in patients with more severe chronic hypokalaemia (plasma potassium ranged between 2.6 and 3.4 mmol/l or more in our patients) or hypomagnesaemia (plasma magnesium ranged between 0.50 and 0.70 mmol/l in our patients), in the context of acute disease conditions like diarrhoea or vomiting that further exacerbate hypokalaemia, in the context of alcoholism, a well recognized cause of hypomagnesaemia [7], and during medication with drugs that prolong the QT interval [6]. Short-term non-adherence to the recommended regimen of care is a further possible cause of dangerous cardiac arrhythmias in Gitelman syndrome, considering the gastrointestinal side effects regularly occurring during supplementation with potassium or
magnesium [19]. This impression is supported by the results of an inquiry among a group of European paediatric nephrologists with a large experience in the field of Gitelman syndrome [20]. Their impression is further supported by the case of a child with an unclassifiable form of renal hypokalaemia, who suddenly died [21], by that of a newborn with severe hypokalaemia of renal origin who developed cardiac arrhythmias followed by cardiac arrest [22], and by the fact that the risk of sudden death is increased in adult patients with essential hypertension who experience mild hypokalaemia (potassium levels ranging from 3.0 to 3.4 mmol/l) on long-term medication with thiazides [23].

Recent observations state that potassium depletion with or without concurrent magnesium depletion impairs cardiac performance in normal dogs and healthy human volunteers and facilitates coronary artery thrombosis in vitro [9]. Little is known on myocardial function in patients with hereditary renal hypokalaemia, with the exception of a case report of an adult patient with a severe, lethal cardiomyopathy [24]. In addition, the myocardial contractile reserve has been noted to be slightly but significantly impaired in six patients aged from 19 to 48 years with chronic renal hypokalaemia [25]. In our patients with chronic hypokalaemia and hypomagnesaemia left ventricular volume and mass, left ventricular systolic function and left ventricular diastolic function were not altered. Furthermore, we failed to disclose electrocardiographic features suggestive of myocardial ischaemia. Our data are supported by the results of a small study in five children suffering from chronic hypokalaemia, whose echocardiographic assessment did not reveal any abnormal myocardial function [26]. The discrepancy between our data, respectively, the observations in children with chronic hypokalaemia on the one side and the observations in the patients with lethal cardiomyopathy, respectively, impaired myocardial contractile reserve on the other side is likely related to the fact that patients with cardiomyopathy, respectively, impaired myocardial contractile reserve tended to be more hypokalaemic and older than our patients and the five afore mentioned children with chronic hypokalaemia.

In conclusion, this systemic cardiac work up in patients with mild to moderate hypokalaemia and hypomagnesaemia secondary to Gitelman syndrome did not detect significant abnormalities of cardiac rhythm and abnormal myocardial morphology or function on echocardiography and Doppler assessment. We feel strongly that the data do not exclude that severe cardiac arrhythmias and myocardial dysfunction might sometimes occur in Gitelman syndrome or in related hypokalaemic tubulopathies. A long-term follow up to see whether these patients have an increased cardiovascular morbidity or an international inquiry might perhaps provide some answer to the question.

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Conflict of interest statement. None declared.

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