Hypocalcaemic cardiomyopathy: a description of two cases and a literature review

Martin Válek\textsuperscript{1}\textsuperscript{*}, Lenka Roblová\textsuperscript{1}, Ivan Raška Jr.\textsuperscript{2}, Dita Schaffelhoferová\textsuperscript{3} and Tomáš Paleček\textsuperscript{1}

\textsuperscript{1}Second Department of Medicine, Department of Cardiovascular Medicine, General University Hospital in Prague and First Faculty of Medicine, Charles University, Prague, Czech Republic; \textsuperscript{2}Third Department of Medicine, Department of Endocrinology and Metabolism, General University Hospital in Prague and First Faculty of Medicine, Charles University, Prague, Czech Republic; \textsuperscript{3}Department of Cardiology, Heart Center, České Budějovice Hospital, České Budějovice, Czech Republic

Abstract

Hypocalcaemic cardiomyopathy is a rare form of dilated cardiomyopathy. The authors here present two cases in which symptomatic dilated cardiomyopathy was the result of severe hypocalcaemia. First, we report about a 26-year-old woman with primary hypoparathyroidism and then about a 74-year-old man with secondary hypoparathyroidism following a thyroidectomy. In both cases, the left ventricular systolic function improved after calcium supplementation. In the first case, a lack of compliance led to a repeated decrease of both serum calcium level and left ventricular systolic function. The authors also present a comprehensive summary of all cases of hypocalcaemic dilated cardiomyopathy that have been described in literature to date. The mean age of the affected patients was 48.3 years, of which 62\% were female patients. The most common causes of hypocalcaemic cardiomyopathy are primary hypoparathyroidism (50\%) and post-thyroidectomy hypoparathyroidism (26\%). In the post-thyroidectomy subgroup, the median time for the development of hypocalcaemic cardiomyopathy is 10 years (range: 1.5 months to 36 years). Hypocalcaemic cardiomyopathy leads to heart failure with reduced ejection fraction in 87\% of patients. Generally, the most common complications of hypoparathyroidism and/or hypocalcaemia are cerebral calcifications, cognitive deficit, and cataracts. Once calcium supplementation is administered, the disease has a good prognosis and, in most individuals, a significant improvement (21\%) or even normalization (74\%) of the left ventricular systolic function occurs.

Keywords Dilated cardiomyopathy; Hypocalcaemia; Calcium; Parathormone; Hypoparathyroidism; Heart failure

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Introduction

Hypocalcaemic cardiomyopathy is considered to be a very rare cause of heart failure with reduced left ventricular (LV) ejection fraction (EF). This article reports the first two cases of hypocalcaemic cardiomyopathy that have been described in the Czech Republic. A description of the first case was published in the regional journal of the Czech Society of Cardiology ‘Cor et Vasa’.\textsuperscript{1} However, because this case clearly describes the typical course of hypocalcaemic cardiomyopathy, we are also presenting it in this article. The second case in this article is being described for the first time. In addition, this article provides a summary of the largest number of cases published, describing the specifics of this type of heart failure and attempting to explain why hypocalcaemic cardiomyopathy is so rare, even though hypocalcaemia is a frequent finding.

Case report 1

A 26-year-old woman was diagnosed with hypoparathyroidism in 2017 based on symptoms of paraesthesia and upper limb convulsions. Because of her limited intelligence, she was not taking any prescribed medication nor attending any physician’s check-ups. In May 2018, she was admitted to our hospital presenting with acute shortness of breath. The physical examination revealed short posture (158 cm), cachectic

\textsuperscript{*}Correspondence to: Martin Válek, Second Department of Medicine, Department of Cardiology and Angiology, General University Hospital in Prague and First Faculty of Medicine, Charles University, U Nemocnice 2, Prague 2, 128 08, Czech Republic. Tel: +420 224 962 605; Fax: +420 224 912 154. Email: m.valek@seznam.cz

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habitus, and heavily carious teeth (Figure 1). Her blood pressure was 75/50 mmHg, and her heart rate was regular at 80 bpm. The electrocardiogram showed a sinus rhythm with QTc of 575 ms. Echocardiographic examination found a dilated left ventricle with a severely depressed EF of 25% because of diffuse hypokinesis. The LV diastolic function was also severely impaired. Only mild mitral and tricuspid regurgitations were present, and the estimated pulmonary artery systolic pressure was within the normal range. Cardiac magnetic resonance did not demonstrate any signs of myocardial inflammation or replacement fibrosis. The computed tomography coronary angiography was normal. Laboratory tests showed an unmeasurably high N terminal pro-BNP level, as well as signs of renal and liver dysfunction. Importantly, advanced hypocalcaemia, hypomagnesaemia, and hyperphosphataemia were also found. Other possible causes of hypocalcaemia except hypoparathyroidism were not identified. An ophthalmologist’s examination revealed an incipient cataract. Cerebral calcifications were not present on the computed tomography scan.

Based on these findings, the diagnosis of acute heart failure because of the hypocalcaemic dilated cardiomyopathy associated with untreated hypoparathyroidism was made. The patient was treated with typical heart failure therapy together with calcitriol administration, and calcium and magnesium supplementation. At the end of the hospitalization, the patient was completely asymptomatic, and her blood ion levels were normal (Table 1).

In September 2018, the patient could tolerate exertion without restrictions, and the peeling, dry skin had disappeared. The LV systolic function was improved with an EF of 42%, as described by echocardiography. However, both the calcium and magnesium blood levels had decreased significantly (Table 1). To rule out impaired absorption of the orally administered calcium and magnesium, the patient was admitted to the hospital, where peroral hypoparathyroidism treatment was administered for 7 days. Importantly, she was not treated with heart failure medication at this time. During this short time period, there was a significant improvement and even normalization of hypocalcaemia, hypomagnesaemia,

**Table 1** Patient 1 laboratory values

|                              | May 2018 (admission) | May 2018 (discharge) | September 2018 | November 2018 (admission) | November 2018 (discharge) | December 2019 | Reference range |
|------------------------------|----------------------|----------------------|----------------|---------------------------|---------------------------|---------------|-----------------|
| Calcium total (mmol/L)       | 1.19                 | 2.42                 | 1.23           | 1.21                      | 1.64                      | 0.99          | 2.00–2.75       |
| Calcium ionized (mmol/L)     | 0.64                 | 1.22                 | 0.62           | 0.60                      | 0.87                      | 0.56          | 1.13–1.32       |
| Phosphate (mmol/L)           | 3.22                 | 1.7                  | 2.24           | 2.08                      | 2.16                      | 2.37          | 0.65–1.61       |
| Magnesium (mmol/L)           | 0.53                 | 0.79                 | 0.41           | 0.35                      | 0.61                      | 0.35          | 0.70–1.00       |
| PTH (pmol/L)                 | 0.58                 | 0.58                 | 0.58           | 0.58                      | 0.58                      | 0.58          | 1.58–6.03       |
| 1,25-OH vitamin D (ng/L)     | 6.2                  | 14.4                 | 14.4           | 25.6                      | 32.6                      | 32.3          | 19.9–79.3       |
| 25-OH vitamin D (ng/ml)      | 22.3                 | 31.6                 | 31.6           | 32.3                      | 32.3                      | 17.5          | 30.0–60.0       |
| NT-proBNP (ng/L)             | >35 000              | 807                  |                | 2161                      |                            | 0–125         | 0–125           |
| High sensitive troponin I (μg/L) | 36.4               | 3.1                  | 3.5            |                           |                           | 0–11.6        |                 |
| CRP (mg/L)                   | 61.7                 | 1.1                  | <1.0           | 1.7                       | 3.3                       | 3.3           | 0–5            |
| Creatinin (μmol/L)           | 279                  | 147                  | 92             | 99                        | 101                       | 91            | 44–104          |
| Aspartate transaminase (ukat/L) | 15.72              | 0.22                 | 0.54           | 0.29                      | <0.2                      | 0.48          | 0.10–0.72       |
| Alanin transaminase (ukat/L) | 22.22                | 0.62                 | 0.29           | <0.1                      | 0.2                       | 0.21          | 0.10–0.72       |

1,25-OH vitamin D, 1,25-dihydroxycholecalciferol; 25-OH vitamin D, 25-hydroxycholecalciferol; CRP, C-reactive protein; NT-proBNP, N terminal pro brain natriuretic peptide; PTH, parathormone; ScvO₂, central venous oxygen saturation.
1,25-OH vitamin D level (Table 1), LV systolic (Figure 2) and diastolic (Figure 3) function. Poor compliance with therapy was therefore presumed to be the cause of the non-improving hypocalcaemia.

At the end of 2019, the blood levels of calcium and magnesium had again decreased significantly. Similarly, LV systolic function had decreased (Tables 1 and 2). The patient remains asymptomatic, but her long-term prognosis is uncertain.

**Case report 2**

A 74-year-old man underwent a total thyroidectomy for goitre in 2009 and curative radiotherapy for prostate cancer in 2013. He was also treated for arterial hypertension and regularly followed-up for stage 3 chronic kidney disease. A low plasma calcium level was also detected in 2014 by a urologist, but no treatment was administered.

In June 2017, the patient was admitted to hospital for several weeks’ lasting dyspnoea NYHA classes II and III. Both the blood pressure and heart rate were within the normal range. The electrocardiogram showed a sinus rhythm with a QTc interval of 450 ms. Echocardiographic examination demonstrated diffuse hypokinesis of non-dilated LV with an EF of 44%. No significant valvular disease was present. A selective coronary angiography did not demonstrate any significant findings. The N terminal pro-BNP level was significantly elevated. The laboratory examination also revealed hypocalcaemia and hyperphosphataemia because of primary hypoparathyroidism.

**Figure 2** The figure shows M mode tracings of the left ventricle that demonstrate significant improvement of left ventricular systolic function in November 2018 when the patient received oral treatment of hypoparathyroidism under supervision.

**Figure 3** The figure depicts a noticeable increase of early diastolic septal mitral annular velocity (e') in November 2018, reflecting the improvement in myocardial relaxation properties when the patient received oral treatment of hypoparathyroidism under supervision.
hypoparathyroidism (Table 3). The diagnosis of left-sided heart failure because of hypocalcaemic dilated cardiomyopathy was established, and heart failure therapy as well as calcium supplementation were initiated.

However, the patient arbitrarily stopped taking the medication and was repeatedly hospitalized for heart failure decompensation during the following months. A severe decrease in LV systolic function with EF of 26% was found (Table 4). The status was further complicated by an acute kidney injury requiring acute haemodialysis in June 2018. At that time, both the hypocalcaemia and hyperphosphataemia worsened, and hypomagnesaemia was also diagnosed (Table 3). The treatment of hypoparathyroidism was restored, with resulting improvement of the patient’s condition in a few days. At the 3 month follow-up, in September 2018, the patient did not report any heart failure symptoms. He declared having taken all of the prescribed medication targeting hypoparathyroidism and heart failure. Laboratory values of calcium phosphate metabolism were within the normal range, and echocardiographic examination demonstrated significant improvement in the LV systolic function with an EF of 52% (Table 4).

| Table 2 Patient 1 echocardiographic parameters |
|-----------------------------------------------|
| May 2018 | June 2018 | September 2018 | November 2018 (admission) | November 2018 (discharge) | January 2019 | December 2019 |
|--------|----------|---------------|--------------------------|--------------------------|-------------|--------------|
| EDD (mm) | 55 | 55 | 50 | 52 | 50 | 51 | 54 |
| EDD/BSA (mm/m²) | 42 | 42 | 35 | 37 | 35 | 36 | 38 |
| EDV (mL) | 130 | 102 | 115 | 102 | 102 | 90 | 98 |
| EF (%) | 25 | 42 | 39 | 43 | 52 | 48 | 33 |
| E gradient (mmHg) | 1.2 | 2.0 | 0.94 | 0.93 | 0.95 | 0.96 | 0.75 |
| A gradient (mmHg) | 0.49 | 0.4 | 0.43 | 0.5 | 0.54 | 0.38 | 0.58 |
| E/A ratio | 2.45 | 2.25 | 2.19 | 1.86 | 1.75 | 2.53 | 1.29 |
| a’ septal/lateral (m/s) | 0.07/0.05 | 0.04/0.04 | 0.03/0.04 | 0.04/0.04 | 0.04/0.05 | 0.04/0.05 |
| E/e’ | 13.3 | 6.7 | 4.1 | 7.8 | 5.9 | 6.6 | 8.0 |

BSA, body surface area; EDD, end diastolic diameter; EDV, end diastolic volume; EF, ejection fraction; ESD, end systolic diameter.

Summary of current literature on hypocalcaemic cardiomyopathy

The PubMed database was searched in November 2019 using the keywords ‘hypocalcaemia AND cardiomyopathy’ and ‘hypocalcaemia AND heart failure’, as well as using references found in the articles. Only articles in English were included, with the exception of the first published case, which was published in German. The reports on patients < 18 years were excluded. Only symptomatic heart failure cases were included in the evaluation. Our two cases were also included in the overall evaluation. A total of 57 articles describing 61 cases were found.2–58 All publications were independently evaluated by two researchers (M. V. and L. R.).

Heart failure was divided according to the Guidelines of the European Society of Cardiology for heart failure with reduced EF (EF < 40%; HFrEF), mid-range EF (EF 40–49%; HFrEF), and preserved EF (EF ≥ 50%).59 The improvement of the LV systolic function was defined as an absolute increase ≥10% (i.e. 10 percentage points) in the LVEF60 or as an improvement of the LVEF ≥ 50%. Only publications that stated the baseline LVEF numerically (n = 39) were included in the evaluation of the initial heart failure type. Those publications reporting both the baseline and final LVEF numerically (n = 33) or verbally indicated EF improvement/normalization (n = 4) were included in the outcome evaluation. Several

| Table 3 Patient 2 laboratory values |
|------------------------------------|
| July 2017 | June 2018 | September 2018 | Reference range |
|--------|----------|---------------|----------------|
| Calcium total (mmol/L) | 1.52 | 1.06 | 2.1 | 2.10–2.65 |
| Phosphate (mmol/L) | 1.8 | 2.2 | 1.5 | 0.7–1.6 |
| Magnesium (mmol/L) | 0.77 | 0.6 | 0.7–1.07 |
| PTH (pmol/L) | 1 | 2.0–9.3 |
| NT-proBNP (ng/L) | 2052 | 22 000 | 0–450 |
| Creatinine (μmol/L) | 126 | 181 | 130 | 64–104 |
| Albumin (g/L) | 47 | 35–53 |
| TSH (mU/L) | 1.2 | 1.57 | 0.55–4.78 |
| fT₄ (pmol/L) | 20.7 | 21.7 | 11.5–22.7 |

CRP, C-reactive protein; fT₄, free thyroxine; NT-proBNP, N terminal pro brain natriuretic peptide; PTH, parathormone; TSH, thyroid-stimulating hormone.

| Table 4 Patient 2 echocardiographic parameters |
|-----------------------------------------------|
| June 2018 | September 2018 |
|--------|-------------|
| EDD (mm) | 63 | 58 |
| ESD (mm) | 52 | 42 |
| EDV (mL) | 201 |
| Left ventricular ejection fraction (%) | 26 | 52 |
| Right ventricular end-diastolic dimension (mm) | 46 | 34 |
| Right atrial area (cm²) | 31.1 | 26.5 |
| Mitral regurgitation, grade (1–4) | 2–3 | 2 |
| Tricuspid regurgitation peak gradient (mmHg) | 40 | 23 |

BSA, body surface area; EDD, end diastolic diameter; EDV, end diastolic volume; EF, ejection fraction; ESD, end systolic diameter.
methods (echocardiography, invasive ventriculography, and scintigraphy) were used for the evaluation of LVEF in the literature reviewed. LV diastolic function, right ventricular function, and other echocardiographic parameters were only sporadically reported in the published articles and thus not completely evaluated in our review.

**Discussion**

The first case report of hypocalcaemic cardiomyopathy was described in 1939 by Hegglin38 of a 51-year-old female patient with a history of goitre surgery and presenting with congestive heart failure. The sole administration of dihydrotachysterol (AT 10) resulted in an improvement of diuresis as well as symptom relief.

Hypocalcaemic cardiomyopathy is considered to be a rare disease. To our best knowledge, 61 cases have been described so far. The basic characteristics of these patients, as well as our cases, are summarized in Table 5. The described cases of hypocalcaemic cardiomyopathy show a slight predilection for the female gender (62%). The mean age of the affected patients is 48.3 years.

**Aetiology**

The rareness of hypocalcaemic cardiomyopathy is surprising because hypoparathyroidism and hypocalcaemia are much more frequent. The prevalence of hypocalcaemia because of hypoparathyroidism in adults is reported to be 20–40 cases per 100 000 people.61–63 Previous studies have considered a possible explanation of hypocalcaemic cardiomyopathy being a late manifestation of long-lasting hypocalcaemia.2,30 In most patients, the symptoms of hypocalcaemia that would lead to treatment initiation would probably have appeared earlier. This hypothesis is supported by data from the collected case reports. In primary hypoparathyroidism, it is difficult to determine the exact duration of hypocalcaemia. However, in patients after surgery, the interval between surgery and the development of hypocalcaemic cardiomyopathy can be easily ascertained. In a subgroup of 16 individuals with a history of thyroidectomy, the median time for the development of hypocalcaemic cardiomyopathy was 10 years, with a range of 1.5 months to 36 years.

Generally, the most common cause of hypoparathyroidism is the post-thyroidectomy condition that makes up 80–90% of cases.61–64 Interestingly, the development of hypocalcaemic cardiomyopathy is most commonly related to idiopathic hypoparathyroidism (Figure 4). As idiopathic hypoparathyroidism is difficult to diagnose and patients after thyroidectomy receive regular check-ups, hypocalcaemia in idiopathic hypoparathyroidism may take longer to be diagnosed.

In some patients, symptoms of hypocalcaemia do not appear for reasons that are unclear. However, some individuals have unrecognized symptoms of hypocalcaemia. A few patients had been erroneously diagnosed with epilepsy or epileptiform seizures.10,11,21,25 Some patients were also insufficiently treated, or they showed poor cooperation.2,21,42,46

**Pathophysiology**

The exact pathophysiology of hypocalcaemic cardiomyopathy has not been yet clarified. The lack of calcium is not the only mechanism that leads to the development of heart failure, although its low levels play a key role. Intracellular changes in calcium concentrations are essential for myocyte activity, as the transfer of calcium from the extracellular into the intracellular space triggers a chain reaction that ends in myocyte contraction. The increase of intracellular calcium concentration transiting through calcium channels is followed by calcium release from sarcoplasmic reticulum, its binding to the troponin–tropomyosin complex, and stimulation of the mutual binding of actin and myosin.65 Additionally, in contrast to striated myocytes, the activity of cardiac myocytes is directly dependent on the calcium concentration in the extracellular fluid.66

Vitamin D deficiency may have a direct effect on the development of myocardial dysfunction. In rat experiments, vitamin D deficiency was associated with the development of cardiac hypertrophy and fibrosis.67 The mechanism leading to the described changes consists of decreased renin production and the subsequent increased activity of the renin–angiotensin system.68,69 Epidemiological studies in humans have shown that low levels of vitamin D are linked to LV systolic dysfunction, a higher risk of developing heart failure, increased mortality, and sudden death.70–72

Parathormone (PTH) has an independent apparent influence as it directly affects the L-calcium ion channels in the myocardium and also has a positive chronotropic effect in neonatal cells.73

Magnesium also plays a role in the pathophysiology of calcium and phosphate metabolism. Its low levels are often observed in patients with hypocalcaemic cardiomyopathy. Magnesium contributes to the regulation of PTH secretion. Mild hypomagnesaemia stimulates PTH secretion, but severely low levels of magnesium (<0.5 mmol/L) are associated with a paradoxical block of PTH secretion.74,75 Based on this mechanism, pronounced hypomagnesaemia could be one of the causes of hypoparathyroidism resistant to the administration of calcium. Nevertheless, magnesium supplementation leads to an increase of PTH within a few minutes.76 In the published case reports, 41% of the patients had low plasma levels of magnesium (<0.7 mmol/L), but only two patients, described in Case Report 1 and by Andreozzi et al.,52 reached a value below 0.5 mmol/L. However, even after the

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Table 5  Summarization of the basic characteristics of cases described in literature from 1939 to November 2019

| Author     | Journal             | Year | Age (years) | Sex      | Aetiology of hypocalcaemia                  | Hypocalcaemia duration | Arrhythmia/ECG changes                      |
|------------|---------------------|------|-------------|----------|---------------------------------------------|------------------------|---------------------------------------------|
| Hegglin    | Helvetica Medica Acta | 1939 | 51          | Female   | Thyreoidectomy                              | 25 years              |                                             |
| Evans      | Lahey Clin Bull     | 1945 | 43          | Male     | Primary hyperparathyroidism                 | Unknown                |                                             |
| Jernigan   | Stanford Med Bull   | 1953 | 58          | Female   | Primary hyperparathyroidism                 | 27 years              | Premature ventricular contractions          |
| Grieve     | SA Medical J        | 1955 | 38          | Female   | Primary hyperparathyroidism                 | 3 years                | Long QT                                     |
| Sussman    | NEJM                | 1957 | 52          | Male     | Primary hyperparathyroidism                 | Unknown                | Long QT                                     |
| Falko      | Am J Med Sci        | 1976 | 19          | Male     | Primary hyperparathyroidism                 | 10 days                |                                             |
| Brenton    | Postgrad Med J      | 1978 | 35          | Male     | Primary hyperparathyroidism                 | Unknown                | Long QT                                     |
| Bashour    | Chest               | 1980 | 35          | Female   | Idiopathic hypocalcaemia                    | At least 7 years       | Long QT                                     |
| Murros     | Acta Med Scand      | 1980 | 18          | Female   | Thyreoidectomy                              | 1.5 years              | Incessant polymorphic ventricular tachycardia |
| Giles      | Chest               | 1981 | 47          | Female   | Thyreoidectomy                              | 5 years                | Long QT                                     |
| Connor     | NEJM                | 1982 | 76          | Female   | Primary hyperparathyroidism                 | 9 months               |                                             |
| Levine     | Am J Med            | 1985 | 39          | Female   | Thyreoidectomy                              | 10 years               | Long QT                                     |
| Rimailho   | Am Heart J          | 1985 | 61          | Male     | Primary hyperparathyroidism                 | Unknown                | Long QT                                     |
| Varthakavi | In Heart J          | 1985 | 44          | Female   | Parathyreoidectomy                          | 3 days                 | Long QT                                     |
| Huddle     | SAMJ                | 1987 | 39          | Female   | Primary hyperparathyroidism                 | 9 years                | Long QT                                     |
| Huddle     | SAMJ                | 1987 | 58          | Female   | Primary hyperparathyroidism                 | Unknown                | Long QT                                     |
| Huddle     | SAMJ                | 1987 | 38          | Female   | Unknown                                     | At least 6 months      | Long QT                                     |
| Csanády    | Br Heart J          | 1990 | 25          | Female   | Primary hyperparathyroidism                 | Unknown                | Long QT                                     |
| Mano       | Jpn J Med           | 1991 | 65          | Male     | Primary hyperparathyroidism                 | At least 20 years      | Non-sustained ventricular tachycardia, atrial fibrillation, long QT |
| Kudoh      | Int Med             | 1992 | 46          | Male     | Primary hyperparathyroidism                 | At least 20 years      | Non-sustained ventricular tachycardia, atrial fibrillation, long QT |
| Shinoda    | Nephron             | 1992 | 60          | Male     | Parathyreoidectomy                          | 1 day                  | At least 2 years                            |
| Rallidis   | Int J Cardiol       | 1997 | 46          | Female   | Primary hyperparathyroidism                 | 1 year                 | Long QT                                     |
| Suzuki     | Clin Cardiol        | 1997 | 53          | Female   | Primary hyperparathyroidism                 | At least 10 years      | Long QT                                     |
| Lehmann    | Chest               | 2000 | 25          | Female   | Primary hyperparathyroidism                 | At least 1.5 years     | Long QT                                     |
| Fisher     | Eur J Heart Failure | 2001 | 38          | Male     | Parathyreoidectomy                          | 3 weeks                | Long QT                                     |
| Nasser     | CHF                 | 2001 | 55          | Male     | Primary hyperparathyroidism                 | 3 years                | Long QT                                     |
| Altunbas   | Horm Res            | 2002 | 46          | Female   | Thyreoidectomy                              | 12 years (treated only in symptomatic hypocalcaemic episodes) At least 2 years | Atrial fibrillation, long QT               |
| Altunbas   | Horm Res            | 2003 | 55          | Male     | Thyreoidectomy                              | 19 years (treated only in symptomatic hypocalcaemic episodes) 3 years | Atrial fibrillation, long QT               |
| Avsar      | Echocardiography    | 2004 | 40          | Female   | Thyreoidectomy                              | 3 years                | Junctional tachycardia, long QT             |
| Hurley     | J Emerg Med         | 2005 | 73          | Male     | Primary hyperparathyroidism                 | Unknown                | Atrial fibrillation, long QT               |
| Tsironi    | Int J Hematology    | 2005 | 25          | Male     | Hemosiderosis-beta-thalasemia              | Unknown                | Atrial fibrillation, long QT               |

(Continues)
Table 5 (continued)

| Author       | Journal                  | Year | Age (years) | Sex | Aetiology of hypocalcaemia          | Hypocalcaemia duration | Arrhythmia/ECG changes                  |
|--------------|--------------------------|------|-------------|-----|------------------------------------|------------------------|----------------------------------------|
| Tziomalos    | Clin Endocrin            | 2006 | 68          | Male| Primary hyperparathyroidism        | Unknown                | Atrial fibrillation, long QT           |
| Gupta        | JAPI                     | 2007 | 18          | Male| Primary hyperparathyroidism        | Unknown                | Long QT                                |
| Chavan       | Annals Int Med           | 2007 | 48          | Male| Vitamin D deficiency              | Unknown                | Monomorphic and polymorphic ventricular tachycardia, long QT |
| Kazmi        | Am J Med Sci             | 2007 | 71          | Female| Thyreoidectomy                      | 4 years                | Long QT                                |
| Broncel      | Arch Med Sci             | 2010 | 60          | Female| Primary hyperparathyroidism        | Unknown                | Long QT                                |
| Jariwala     | JAPI                     | 2010 | 24          | Male| Primary hyperparathyroidism        | Unknown                | Long QT                                |
| Lekas        | Adv Perit Dial           | 2010 | 27          | Female| Parathyroidectomy                   | 8 months               | Long QT                                |
| Mavroudis    | Clin Cardiol             | 2010 | 39          | Male| Hypoparathyrosis-coeliac disease   | Unknown                | Long QT                                |
| Solzbach     | Herz                     | 2010 | 61          | Male| Thyreoidectomy                      | 6 months               | Long QT                                |
| Sung         | J Cardiovasc Ultrasound  | 2010 | 57          | Female| Primary hyperparathyroidism        | Unknown                | Long QT                                |
| Babu         | Indian J Endocrinol Metab| 2011 | 70          | Female| Primary hyperparathyroidism        | Unknown                | Long QT                                |
| Behaghel     | Eur J Echocar            | 2011 | 76          | Female| Thyreoidectomy                      | 25 years               | Long QT                                |
| Ballane      | Eur J Endokrin           | 2012 | 56          | Female| Thyreoidectomy                      | 21 years               | Long QT                                |
| Ipek         | Herz                     | 2013 | 24          | Female| Thyreoidectomy                      | 1 year                 | Long QT                                |
| Jung         | Korean J Intern Med      | 2013 | 50          | Female| Primary hyperparathyroidism        | Unknown                | Long QT                                |
| Rhee         | Korean Circ J            | 2013 | 69          | Female| Primary hyperparathyroidism        | 5 years                | Long QT                                |
| Bansal       | J Clin Endocrinol Metab  | 2014 | 47          | Female| Primary hyperparathyroidism        | 5 years                | Long QT                                |
| Jeong        | Endocrinol Metab         | 2014 | 29          | Female| Hemosiderosis                       | 10 years               | Long QT                                |
| Vlot         | BMJ Case rep             | 2014 | 59          | Female| Primary hyperparathyroidism        | Unknown                | Long QT                                |
| Vlot         | BMJ Case rep             | 2014 | 68          | Female| Thyreoidectomy                      | Unknown                | Long QT                                |
| Jamieson     | J R Coll Physicians Edinb| 2015 | 45          | Male| Digeorge syndrome - 22q11.21 deletion| 5 years                | Long QT                                |
| Venugopalan  | JAGS                     | 2015 | 87          | Male| Vitamin D deficiency               | Unknown                | Ventricular tachycardia, Long QT       |
| Batra        | J Ass Physicians India   | 2016 | 68          | Female| Vitamin D deficiency               | Unknown                | Long QT                                |
| Elikowski    | Pol Merkur Lekarsi       | 2017 | 60          | Male| Thyreoidectomy                      | 36 years               | Long QT                                |
| Andreozzi    | Eur J Case Rep Intern Med| 2018 | 56          | Female| Unknown                            | Unknown                | Long QT                                |
| Kadeli       | J Assoc Physicians India | 2018 | 34          | Female| Thyreoidectomy                      | 5 years                | Long QT                                |
| de Oliveira  | Clinical Case Reports    | 2019 | 54          | Female| Primary hyperparathyroidism        | Unknown                | Long QT                                |
| Martins Duarte| Clinical Case Reports   | 2019 | 22          | Male| Pseudohyoparathyroidism            | At least 5 years       | Long QT                                |
| Fasih        | Eur J Case Rep 12 Intern Med| 2019 | 40          | Female| Thyreoidectomy                      | 6 years                | Long QT                                |
| Parepa       | Acta Endocrinologica (Buc)| 2019 | 55          | Male| Primary hyperparathyroidism        | Unknown                | Long QT                                |
| Saini        | BMJ Case Rep             | 2019 | 74          | Male| Thyreoidectomy                      | 8 years                | Long QT                                |
| Schaffelhoferová Cor Vasa | ESC Heart Failure    | 2020 | 26          | Female| Primary hyperparathyroidism        | Unknown                | Long QT                                |

ECG, echocardiogram.
supplementation of magnesium level to normal values, the PTH level did not increase in our Case 1 and thus the hypoparathyroidism appears unlikely to have been caused by severe hypomagnesaemia in this particular patient. Only in Andreozzi’s case was the hypocalcaemia possibly secondary to hypomagnesaemia.

Generally, low levels of plasma magnesium are considered to be one of the risk factors for the development of heart failure. Hypomagnesaemia may therefore be an additional risk factor involved in heart failure exacerbation in patients with hypocalcaemic cardiomyopathy.

Other manifestations of hypoparathyroidism/hypocalcaemia

Patients with hypocalcaemic cardiomyopathy have manifestations of hypoparathyroidism and/or hypocalcaemia, which are summarized in Table 6. The most commonly described complications are cerebral calcifications (12 patients), cognitive deficit (11 patients), and cataracts (12 patients).

The often-occurring cognitive deficit or reduced intelligence is particularly important. Apart from the fact that it is probably another manifestation of prolonged hypoparathyroidism, it is a factor that can significantly delay the patient’s diagnosis, as well as impair their cooperation in the treatment.

Manifestation of hypocalcaemic cardiomyopathy

Based on our literature review, hypocalcaemic cardiomyopathy predominantly leads to HFrEF (in 87% so far described cases), while 11% of patients suffered from HFmrEF, and only one individual had heart failure with preserved EF. Both HFrEF and HFmrEF manifested in 83% of cases as diffuse LV hypokinesia. Regional wall motion abnormalities were described in 10% of individuals, and in two cases, the LV kinetics resembled Takotsubo cardiomyopathy.

The published articles only sporadically described the influence of hypocalcaemia on LV diastolic properties. Case Report 1, in accordance with another article, shows that hypocalcaemia may be associated with significant LV diastolic dysfunction, which may be dramatically improved or even completely normalized with the appropriate therapy (Table 2; Figure 2).

In addition to symptoms of heart failure, hypocalcaemic cardiomyopathy may also manifest with arrhythmias. Atrial fibrillation was documented in three patients, sustained or non-sustained monomorphic and polymorphic ventricular tachycardia in four subjects, ventricular extrasystoles in one individual, and junctional tachycardia in one patient.

Prognosis

The prognosis of hypocalcaemic cardiomyopathy, if treated, is good. In almost three quarters of patients reported so far,
the normalization of LV systolic function was noted, and in a further 21% of individuals, a significant improvement of the LVEF occurred. The LV systolic function remained unimproved in only 5% of patients. Case Report 1 nicely shows that improvement in the LVEF can occur within a few days after plasma calcium level normalization. A rapid improvement of LV systolic properties was also described by Wong et al. in a series of six asymptomatic hypocalcaemic patients who experienced a significant increase in cardiac output after a 1 h long calcium infusion. There may be multiple reasons for the lack of improvement in LV systolic function in a minority of patients. In addition to poor cooperation of the patient, cardiomyocyte degeneration and the development of myocardial fibrosis may also play an important role.

As shown in Case Report 1, the improvement of LV systolic function may be achieved solely by the normalization of calcium and phosphate metabolism, without the administration of conventional heart failure medication. In cases of hypoparathyroidism, this treatment should not be limited to calcium supplementation, which has only a short-term effect, but should also include calcitriol therapy. Treatment with recombiant PTH represents an alternative to calcitriol in case of its insufficient effect. Nevertheless, heart failure therapy is regularly administered in affected patients according to the current guidelines.

So far, only two fatal cases of hypocalcaemic cardiomyopathy have been described. A 76-year-old patient with cognitive deficiency was repeatedly hospitalized for decompensated heart failure. His plasma calcium level could not be compensated, and both dementia as well as cachexia progressed fatally. Another fatal case possibly related to hypocalcaemic cardiomyopathy is that of a 16 years old who died because of an unexplained heart failure and who was the sister of a patient with known idiopathic hypoparathyroidism. There is no evidence that she suffered from hypocalcaemia, but death because of heart failure at such a young age is very rare. Therefore, it can be hypothesized that they both shared a hereditary form of primary hypoparathyroidism that was recognized in only one sibling.

Conclusions

Hypocalcaemic cardiomyopathy is a rare but treatable cause of heart failure with a good prognosis when diagnosed properly. Plasma calcium and magnesium levels and eventually vitamin D level testing should therefore become a routine examination for all patients with unexplained heart failure.

Conflict of interest

None declared.

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