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REVIEW

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

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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'.[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 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.

Figure 1 The picture shows markedly carious dentition and dry peeling skin.

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 administrated 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	1.58–6.03
1,25-OH vitamin D (ng/L)	6.2		14.4	14.4	25.6	33.2	19.9–79.3
25-OH vitamin D (ng/ml)	22.3		31.6	31.6	32.3	17.5	30.0–60.0
NT-proBNP (ng/L)	>35 000		807			2161	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	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
$ScvO_2$ (%)	46.3	68.5					

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; $ScvO_2$, 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

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.

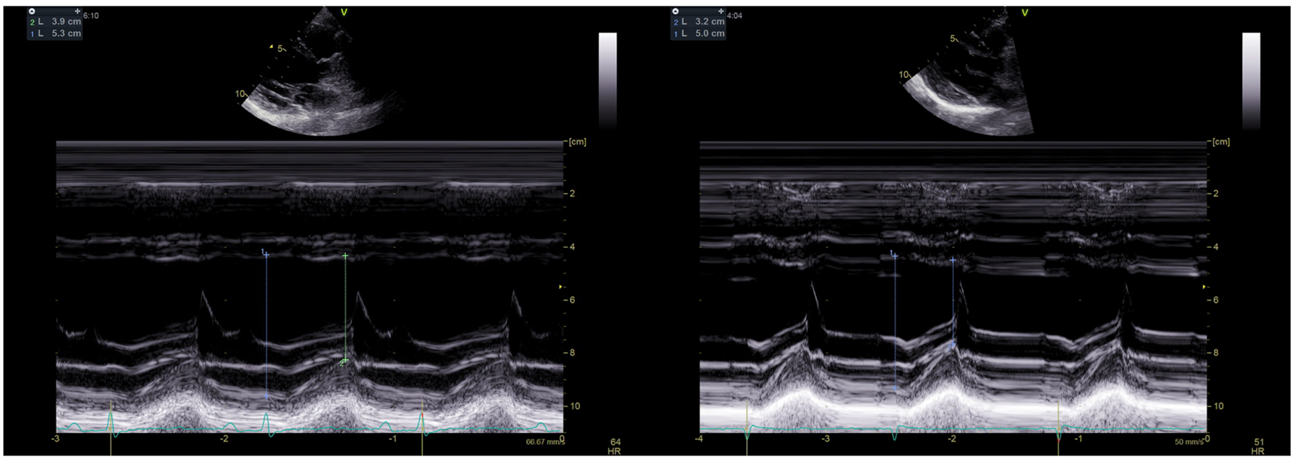

Figure 3 The figure depicts a noticeable increase of early diastolic septal mitral annular velocity (e′) in November 2018, reflecting the improvement in myocardial relaxation properties when the patient received oral treatment of hypoparathyroidism under supervision.

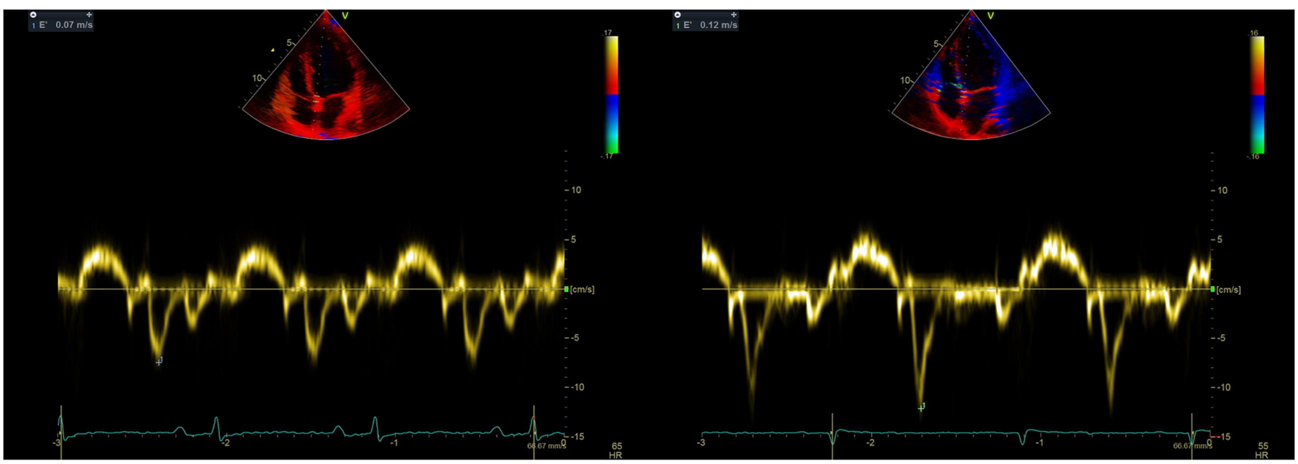

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Table 2 Patient 1 echocardiographic parameters

	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/m^2)	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 (m/s)	1.2	0.9	0.94	0.93	0.95	0.96	0.75
A (m/s)	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
e'septal/lateral (m/s)	0.08/0.1	0.11/0.16	0.08/0.15	0.07/0.17	0.12/0.19	0.09/0.2	0.08/0.13
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	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.

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 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		0.70–1.07
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
fT_4 (pmol/L)	20.7	21.7		11.5–22.7

CRP, C-reactive protein; fT_4, free thyroxine; NT-proBNP, N terminal pro brain natriuretic peptide; PTH, parathormone; TSH, thyroid-stimulating hormone.

Summary of current literature on hypocalcaemic cardiomyopathy

The PubMed database was searched in November 2019 using the keywords 'hypocalcemia AND cardiomyopathy' and 'hypocalcemia 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%; HFmrEF), and preserved EF (EF $\geq$ 50%).[59] The improvement of the LV systolic function was defined as an absolute increase ≥10% (i.e. 10 percentage points) in the LVEF[60] or as an improvement of the LVEF $\geq$ 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 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 (cm^2)	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.

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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 Hegglin[38] 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 ($<$0.5 mmol/L) are associated with a paradoxical block of PTH secretion.[74,75] Based on this mechanism, pronounced hypomagnesaemia could be one of the causes of hypoparathyroidism resistant to the administration of calcium. Nevertheless, magnesium supplementation leads to an increase of PTH within a few minutes.[75] In the published case reports, 41% of the patients had low plasma levels of magnesium ($<$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

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	
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	Female	Primary hyperparathyroidism	Unknown	
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	Parathyroidectomy	1 day	
Rallidis	*Int J Cardiol*	1997	46	Female	Primary hyperparathyroidism	At least 2 years	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	
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)	
Altunbas	*Horm Res*	2003	55	Male	Thyreoidectomy	19 years (treated only in symptomatic hypocalcaemic episodes)	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	Long QT
Tsironi	*Int J Hematology*	2005	25	Male	Hemosiderosis-beta-thalassemia	Unknown	Atrial fibrillation, long QT

(*Continues*)

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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	Parathyreoidectomy	8 months	Long QT
Mavroudis	*Clin Cardiol*	2010	39	Male	Hypoparathyreosis-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	
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	
Ipek	*Herz*	2013	24	Female	Thyreoidectomy	1 year	
Jung	*Korean J Intern Med*	2013	50	Female	Primary hyperparathyroidism	Unknown	Long QT
Rhee	*Korean Circul 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	
Vlot	*BMJ Case rep*	2014	59	Female	Primary hyperparathyroidism	Unknown	
Vlot	*BMJ Case rep*	2014	68	Female	Thyreoidectomy	Unknown	
Jamieson	*J R Coll Phisicians Edinb*	2015	45	Male	Digeorge syndrome - 22q11.21 deletion	5 years	
Venugopalan	*JAGS*	2015	87	Male	Vitamin D deficiency	Unknown	Ventricular tachycardia
Batra	*J Ass Physicians India*	2016	68	Female	Vitamin D deficiency	Unknown	Long QT
Elikowski	*Pol Merkur Lekarski*	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 Martins Duarte	*Clinical Case Reports*	2019	54	Female	Primary hyperparathyroidism	Unknown	
Fasih	*Eur J Case Rep 12Intern Med*	2019	22	Male	Pseudohypoparathyroidism	At least 5 years	
Parepa	*Acta Endocrinologica (Buc)*	2019	40	Female	Thyreoidectomy	6 years	Long QT
Saini	*BMJ Case Rep*	2019	55	Male	Primary hyperparathyroidism	Unknown	Long QT
Schaffelhoferová	*Cor Vasa*	2019	74	Male	Thyreoidectomy	8 years	
Válek	ESC Heart Failure	2020	26	Female	Primary hyperparathyroidism	Unknown	Long QT

ECG, echocardiogram.

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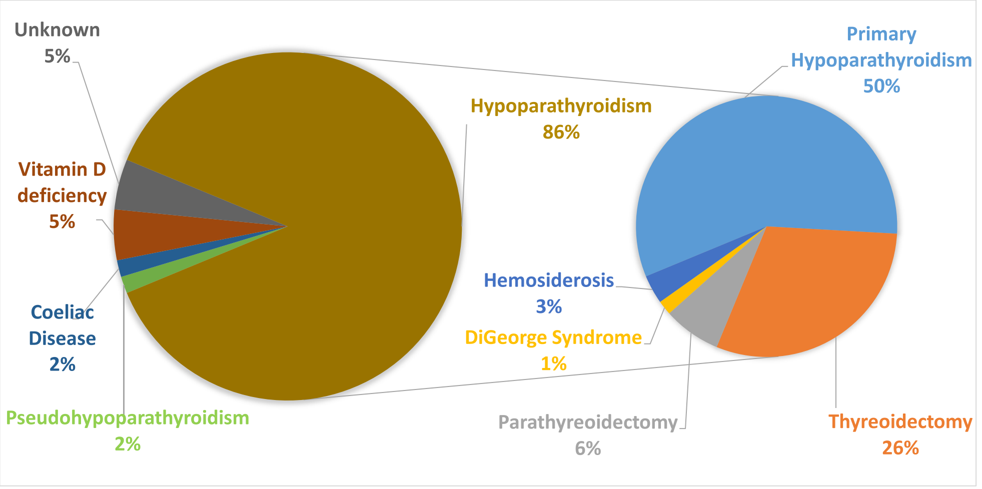
Figure 4 The aetiology of the majority of cases of hypocalcaemic cardiomyopathy is hypoparathyroidism, as shown on the left side of the figure. The right side depicts causes of hypoparathyroidism and shows that primary hypoparathyroidism represents most cases.



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.[76–78] 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,[79,80] 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,[2,8,11,17,32] and only one individual had heart failure with preserved EF.[34]

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.[40,52]

The published articles only sporadically described the influence of hypocalcaemia on LV diastolic properties. Case Report 1, in accordance with another article,[5] 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.[2,3,23,28,30,37,49]

Prognosis

The prognosis of hypocalcaemic cardiomyopathy, if treated, is good. In almost three quarters of patients reported so far,

Table 6 Hypoparathyroidism complications. In addition to complications common to hypoparathyroidism, it is worth noting that four patients were misdiagnosed with epilepsy attributed to hypocalcaemic convulsions

	Patients (*N*)
Brain calcifications	12
Cataract	12
Cognitive dysfunction	11
Teeth destruction	3
'Epilepsy'	4

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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*.[81] 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.[2]

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 recombinant PTH represents an alternative to calcitriol in case of its insufficient effect.[5,82] 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.[12] 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.[13] 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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