

RESEARCH

Is severe hypocalcemia immediately life threatening?

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Abstract

Objective: Severe hypocalcemia (Ca <1.9 mmol/L) is often considered an emergency because of a potential risk of cardiac arrest or seizures. However, there is little evidence to support this. The aim of our study was to assess whether severe hypocalcemia was associated with immediately life-threatening cardiac arrhythmias or neurological complications.

Methods: A retrospective observational study was carried out over a 2-year period in the Adult Emergency Department (ED) of Nantes University Hospital. All patients who had a protein-corrected calcium concentration measure were eligible for inclusion. Patients with multiple myeloma were excluded. The primary outcome was the number of life-threatening cardiac arrhythmias and/or neurological complications during the stay in the ED.

Results: A total of 41,823 patients had protein-corrected calcium (pcCa) concentrations measured, 155 had severe hypocalcemia, 22 were excluded because of myeloma leaving 133 for analysis. Median pcCa concentration was 1.73 mmol/L (1.57–1.84). Seventeen (12.8%) patients presented a life-threatening condition, 14 (10.5%) neurological and 3 (2.2%) cardiac during ED stay. However, these complications could be explained by the presence of underlying co-morbidities and or electrolyte disturbances other than hypocalcemia. Overall, 24 (18%) patients died in hospital. Vitamin D deficiency, chronic kidney disease and hypoparathyroidism were the most frequently found causes of hypocalcemia.

Conclusion: Thirteen percent of patients with severe hypocalcemia presented a life-threatening cardiac or neurological complication on the ED. However, a perfectly valid alternative cause could account for these complications. Further research is warranted to define the precise role of hypocalcemia.

Key Words

- ▶ Severe hypocalcemia
- ▶ emergency department
- ▶ seizures
- ▶ life-threatening arrhythmias

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Introduction

There has been growing interest in hypocalcemia as an independent risk factor for mortality among patients admitted to the emergency department (ED) and ICUs (1, 2, 3, 4). Recently, hypocalcemia has been associated with the risk of sudden cardiac arrest (SCA) in the community (5).

Calcium is a bivalent cation that is essential for a number of physiological processes that include neuromuscular activity, endocrine and exocrine secretion, coagulation, immunity and bone metabolism. Plasma calcium concentration is maintained within a narrow

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range, ~2.2–2.6 mmol/L, despite large movements of calcium across the kidney, bone, gut and cells.

Severe hypocalcemia, defined by a serum calcium <1.9 mmol/L (7.6 mg/dL), is often considered an emergency because of a potential risk of life-threatening cardiac arrhythmias or seizures (6, 7, 8, 9, 10, 11). However, our knowledge of the subject is almost entirely based on case reports (12, 13, 14, 15). These reports often fail to report or simply neglect the role of other variables that could by themselves be responsible for the symptoms and signs attributed to hypocalcemia. For example, dysrhythmias might also be due to concomitant electrolyte abnormalities or medication toxicity and seizures secondary to ischemic brain disease, alcohol withdrawal or tumors.

We have recently described the first series of patients with severe hypercalcemia ($\text{Ca} > 4 \text{ mmol/L}$) admitted to the ED over a 5-year period and found that none presented a severe life-threatening cardiac or neurological complication (16).

To date, there are no published series fully describing hypocalcemic patients and no study has specifically investigated the immediate threat posed by severe hypocalcemia.

The aim of our study was to assess whether severe hypocalcemia ($\text{Ca} < 1.9 \text{ mmol/L}$) was associated with immediately life-threatening cardiac arrhythmias or neurological complications in patients admitted to the ED.

Materials and methods

Patient population and data collection

We carried out a retrospective observational study over a 2-year period, from September 2015 to September 2017 in the Adult ED of Nantes University Hospital (75,000 annual visits).

We identified, using our laboratory database, all patients admitted to the ED who had a calcium concentration measurement. All patients with a protein-corrected calcium concentration <1.9 mmol/L were included. Patients with multiple myeloma were excluded. Patients' records were reviewed, and relevant clinical and biological data were collected. The primary endpoint was the number of life-threatening cardiac arrhythmias and/or neurological complications during the stay in the ED. A life-threatening cardiac arrhythmia was defined by the presence of ventricular tachycardia, ventricular fibrillation, sinus arrest and second-degree or third-degree atrioventricular blocks. A neurological complication was defined by the presence of seizures (before admission or

during ED stay) or a coma with a Glasgow Coma Scale of less than 9/15 (17). The secondary outcomes were correlation between calcium concentrations and the risk life-threatening complications, causes of hypocalcemia and hospital mortality. Total 25 OH vitamin D deficiency was defined as <50 nmol/L (20 ng/mL), hypoparathyroidism by a PTH that was inappropriately low (<20 pg/mL) and hypomagnesemia as <0.6 mmol/L (6, 11, 18).

Because of the retrospective nature of the study, approval by the local ethics committee was not required (articles L.1121-1 paragraph 1 and R1121-2, of the Code of French Public Health). The need for informed consent was waived by the Institutional Review Board of Nantes University Hospital because of the anonymous and purely observational nature of the study.

Biochemical measurements

Blood samples were collected and centrifuged at 2000g for 10 min at 4°C within 1 h after venipuncture. All biochemical measurements of calcium were performed in the same laboratory (Laboratory of Clinical Biochemistry, University Hospital of Nantes) using a photometric CalciumGen.2 assay on the basis of photometric measurements of the calcium–NM-BAPTA complex on Cobasc701 (Roche Diagnostics) according to the manufacturer's instructions. All other biochemical parameters such as total 25 OH vitamin D on LIAISONXL (DiaSorin), total protein and magnesium on Cobasc701 (Roche Diagnostics) and intact parathyroid hormone (PTH) on Cobase602 (Roche Diagnostics) were measured according to the manufacturer's instructions. Protein-corrected calcium (pcCa) levels were estimated as follows: corrected calcium (mmol/L) = measured calcium (mmol/L) / (0.55 + total protein (g/L) / 160) as described previously (19).

Statistical analysis

All data were presented as median and first (Q1) and third (Q3) quartiles. Correlation was tested using Spearman's method and proportions were compared using the χ^2 test (Graph Pad Software Inc.). A *P* value less than 0.05 was considered statistically significant.

Results

Patient selection

A total of 155,259 patients attended the ED over the study period, 41,823 had protein-corrected calcium (pcCa) concentrations measured and 3468 (8.3%) had

hypocalcemia (pcCa < 2.2 mmol/L). One hundred fifty-five patients had severe hypocalcemia (pcCa < 1.9 mmol/L). Twenty-two patients had multiple myeloma and were excluded leaving 133 patients for analysis.

Patient characteristics

The demographic and medical characteristics of the 133 patients, during their stay in the ED, are presented in Table 1. Median age was 70 years (56–81), mean 67.1 ± 16.9 years (range 17–91). The most frequent comorbid states were hypertension (57%), stage 3 to 5 chronic kidney disease (40%), heart failure (38%) and diabetes (38%).

The relevant biological data are presented in Table 2. The median calcium concentration and the median protein-corrected calcium (pcCa) concentration were 1.71 mmol/L (1.56–1.84) and 1.73 mmol/L (1.57–1.84) respectively (Table 2). The median difference between calcium concentration and pcCa was +0.01 mmol/L (mean –0.01 mmol/L, range –0.42 to +0.12 mmol/L). Insufficient biological work-up meant that 29.3% of patients could not be correctly explored. Table 3 details the main causes of hypocalcemia. Vitamin D deficiency, chronic kidney disease (CKD) stages 4/5 and hypoparathyroidism were

Table 1 Demographic and medical characteristics of study population (N = 133).

Number of subjects	133
Age (years)	70 (56–81)
Gender, n female (%)	58 (43.6)
Previous medical history	
Hypertension	76 (57.1)
Chronic kidney disease (stages 3–5)	54 (40.6)
Diabetes	51 (38.3)
Heart failure	51 (38.3)
Hypothyroidism	38 (28.6)
Cervical surgery	37 (27.8)
Cancer	33 (24.8)
Alcohol abuse	30 (22.6)
Cirrhosis	11 (8.3)
Epilepsy	5 (3.8)
Medication	
Statins	54 (40.6)
Proton pump inhibitors	51 (38.3)
Loop diuretics	50 (37.6)
B-Blockers	48 (36.1)
Calcium supplement medication	40 (30.1)
Vitamin D	35 (26.3)
Thiazide diuretics	9 (6.8)
Amiodarone	7 (5.3)
Cinacalcet	6 (4.5)

Results are presented as median (Q1–Q3) or number of patients and proportion (%) when appropriate.

Table 2 Biological characteristics of study population (N = 133).

Calcium (mmol/L)	133 (100)	1.71 (1.56–1.84)
Protein (g/L)	133 (100)	73 (56–78)
Protein-corrected Ca (mmol/L)	133 (100)	1.73 (1.57–1.84)
Magnesium (mmol/L)	89 (66.9)	0.66 (0.41–0.82)
Vitamin D (ng/mL)	61 (45.9)	12.1 (5.8–20)
PTH (pg/mL)	54 (40.6)	77.9 (32.5–164.9)

Results are presented as number of patients and proportion (%) and median (Q1–Q3).

the most frequently found causes of hypocalcemia, representing 34.6, 30.8 and 22.6% respectively. No cause of hypocalcemia was found for 39 patients (29.3%) (Table 3).

Life-threatening events

Seventeen (12.8%) patients presented a life-threatening condition, 14 (10.5%) neurological and 3 (2.2%) cardiac.

Neurological complications were isolated seizures (eight patients), status epilepticus (three patients) and coma (three patients). Neurological complications could be explained by the presence of other co-morbidities and/or other electrolyte disturbances, in all patients but one and are shown in Fig. 1. The only patient with no apparent co-morbidities had no work-up because he left the ED against medical advice. The most frequent abnormalities were hypomagnesemia, alcohol withdrawal syndrome and SNC disease (degenerative, cerebrovascular, tumoral). Only one of the three patients with a history of epilepsy presented with seizures. The three comatose patients were particularly ill, the first presenting a septic shock with multiple organ failure, the second uremic encephalopathy complicating terminal CKD and the third massive post-traumatic cerebral edema resulting in brain death. All three died in less than 48 h.

Table 3 Causes of hypocalcemia found in the study population.

Vitamin D deficiency (<20 ng/mL)	46 (34.5)
Chronic kidney disease ^a	41 (30.8)
Hypoparathyroidism (PTH <20 pg/mL)	30 (22.5)
Post-surgical	16 (12)
DiGeorge syndrome	4 (3)
Autoimmune	3 (2.3)
Cinacalcet	6 (4.5)
Hypomagnesemia (<0.6 mmol/L)	1 (0.7)
Unexplained hypocalcemia	39 (29.3)

Results are presented as number of patients and proportion (%).

^aStages 4 and 5 chronic kidney disease.

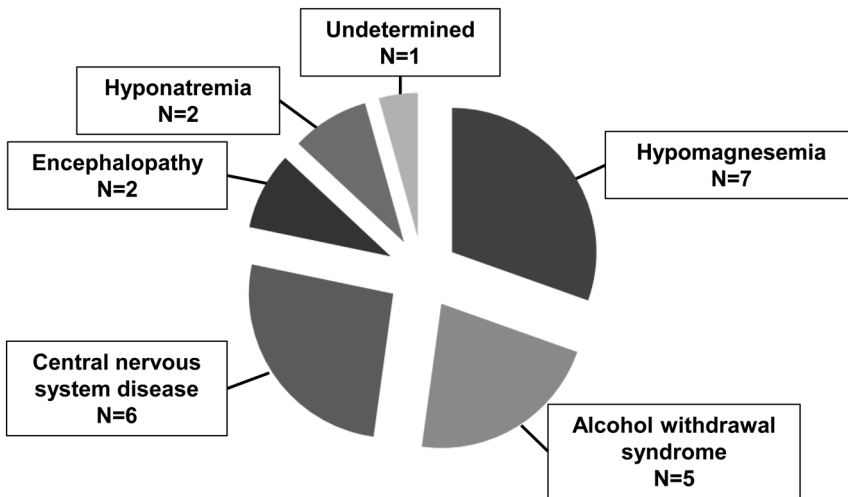


Figure 1
Distribution of the alternative diagnosis for the neurological complications (seizures, coma): Alcohol withdrawal syndrome, central nervous system disease (ischemic, degenerative, traumatic, tumoral), encephalopathy (uremic, septic), hypomagnesemia and hyponatremia.

Cardiac complications were two cardiac arrests (CAs) and one sinus dysfunction. The first CA was due to ventricular fibrillation (VF), in a patient with a repaired tetralogy of Fallot, which responded to defibrillation. The second CA was due to a non-shockable rhythm, which was attributed to severe hypokalemia (1.5 mmol/L), severe acidosis and a massive pulmonary embolism. This patient was the only one to die on the ED. The patient with sinus dysfunction was implanted with a pace maker.

The biological data were analyzed in this subpopulation (patients with life-threatening events). The median calcium of this group was 1.59 mmol/L (1.43–1.75), mean 1.58 ± 0.22 mmol/L (range 1.01–1.88) and was significantly lower than the group of patients that did not have life-threatening complications, median 1.75 mmol/L, mean 1.70 ± 0.18 mmol/L, $P=0.03$ (Fig. 2).

Treatment

Intravenous calcium was administered on the ED to 43 (32%) patients, including 8 of the 17 (47%) patients who presented with a life-threatening complication. The median calcium of the treated group was 1.57 mmol/L (1.41–1.69), mean 1.57 ± 0.18 mmol/L (range 1.05–1.87) and was significantly lower than the group of patients that did not receive IV calcium, median 1.80 mmol/L, mean 1.74 ± 0.16 mmol/L, $P < 0.0001$ (Fig. 3).

Outcome

Out of the 133 patients included, 119 (89.5%) patients were hospitalized, 10 were directly discharged, 3 left against medical advice and as previously stated, 1 patient died on the ED following a non-shockable cardiac arrest.

Twenty-five (18.8%) patients were admitted to ICU, 26 (19.5%) to the nephrology unit, 60 (45.1%) to the general internal medicine ward and 5 (3.8%) to the endocrinology unit. Patients admitted to ICU were severely ill and were not admitted for hypocalcemia.

Median length of hospital stay was 8 days (4–14). Hospital discharge calcium levels were only available for 48/133 (36.1%) patients. Median calcium at discharge was 2.02 mmol/L (1.85–2.2).

Overall, 24 (18%) patients died in hospital, median age was 78.5 years (60.5–83.5) and the median delay before death was 3.5 days (2–8). A subsequent decision to withhold or withdraw life-sustaining therapy and begin palliative care was taken for 18 (75%) of the 24 patients who died. Patients died with multiple organ dysfunction syndrome as a consequence of septic shock (8 patients), heart failure (7 patients) and terminal cancer (4 patients). Median calcium before death (available for 18/24 patients) was 1.80 mmol/L (1.65–1.91). Among the 17 patients

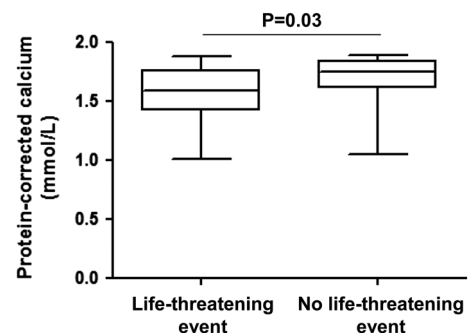
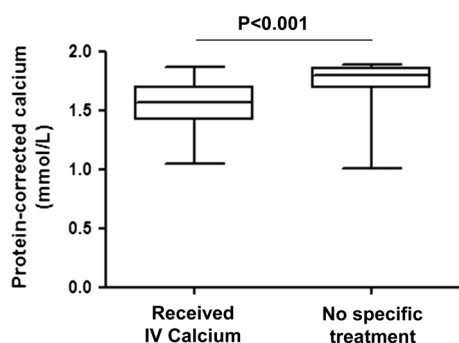


Figure 2
Distribution of pcCa levels in patients with ($n=17$) and without ($n=116$) life-threatening complications. The box extends from Q1 to Q3 quartiles. The line in the middle of the box is plotted at the median and whiskers delimit lowest to highest values.

**Figure 3**

Distribution of pcCa levels in patients who received ($n=43$) or did not receive ($n=90$) IV calcium gluconate in the ED. The box extends from Q1 to Q3 quartiles. The line in the middle of the box is plotted at the median and whiskers delimit lowest to highest values.

who presented life-threatening cardiac conditions or neurological complications, 6 (35%) died.

Discussion

This study is the first to specifically investigate the immediate threat posed by severe hypocalcemia defined by a calcium concentration <1.90 mmol/L. We found that 13% of patients presented immediately life-threatening cardiac or neurological complications on admission to the ED. These patients had lower calcium concentrations than the group of severely hypocalcemic patients with no life-threatening complications. However, pre-existent co-morbidities and/or other electrolyte abnormalities could always account for these complications.

Numerous case reports have associated life-threatening cardiac complications such as reversible heart failure, torsades of pointes, ventricular tachycardia and VF, with hypocalcemia (13). However, these case reports often attribute the rhythm change to hypocalcemia when a perfectly valid differential diagnosis is present. For instance, Gmehlin *et al.* reported a case of VF attributed to hypocalcemia (Ca 1.3 mmol/L) in a 31-year-old patient treated by peritoneal dialysis. This patient also had severe hyperkalemia (K 6.9 mmol/L) and his condition only improved after urgent hemodialysis normalized potassium levels (12).

In 2014, Newman *et al.* published the only review dealing with cardiac dysfunction and hypocalcemia (13). They analyzed 41 individual case reports and 3 case series (2 patients/series) of patients presenting with hypocalcemia (median corrected Ca 1.36 mmol/L) and heart failure or arrhythmias. A significant correlation was found between corrected calcium levels and QTc lengthening.

No correlation was however reported between calcium levels and arrhythmias. The authors concluded that the evidence for reversible cardiac dysfunction associated with hypocalcemia was very limited. They suggested that the development of dysrhythmias was often associated with other co-morbidities such as structural heart disease, ischemia, medication and other electrolyte abnormalities. They also found that most published cases of hypocalcemia were due to secondary hypoparathyroidism following thyroidectomy, and they suggested that abnormalities of thyroid function may have contributed to cardiac dysfunction in these patients.

Recently, attention has focused on the risk of SCA and hypocalcemia (5). Yarmohammadi *et al.* evaluated the role of low calcium levels in the occurrence of SCA in the community. They compared Ca levels (measured within 90 days of SCA) in 267 patients who presented an out-of-hospital cardiac arrest and 445 controls. They found that the group of patients with the lowest Ca (Ca <2.24 mmol/L), had a 2.3-fold increase in odds of SCA when compared to patients with the highest Ca (Ca >2.39 mmol/L). However, there was no significant difference in QT intervals between these two groups, which is unexpected because a lengthening of the QT interval was put forward as a possible explanation for the increased risk of sudden death. This suggests that other unreported factors may be involved such as the existence of elevated parathyroid hormone, thyroid disease, use of QT-modifying medications or abnormal magnesium levels. It is also reasonable to assume that the selected SCA patients, because they were all previously monitored with regard to their Ca levels, had more reasons than average to have abnormal calcemias.

Two patients in our study presented a cardiac arrest. Both had pre-existing conditions, which could by themselves explain the sudden death. The first patient had a previous history of repaired tetralogy of Fallot and presented an episode of VF. Ventricular tachyarrhythmias are known sequelae of this condition. The incidence of sustained ventricular tachycardia and sudden cardiac death in patients 35 years after corrective surgery is 11.9 and 8.3% respectively (20, 21). The second patient had very severe hypokalemia (1.5 mmol/L) and cardiogenic shock from a massive pulmonary embolism. He presented a non-shockable rhythm and died on the ED.

We found a 10% incidence of neurological complications (8% seizures, 2% coma). Our study is the first to highlight the importance of confounding factors potentially implicated in the development of neurological complications. The only other description of neurological

complications occurring in hypocalcemic patients was published by Gupta in 1989 (22). He described a case mix of 81 patients with a Ca ranging from 0.75 to 1.75 mmol/L, seen in an Indian hospital between 1975 and 1987. He found that seizures occurred in 27% of patients, a much higher incidence than in our study. However, he did not mention previous medical history, current medication, associated electrolyte abnormalities (dysnatremia, hypomagnesemia), CNS system disease or alcohol abuse. Indeed the article was mainly based on the description of two illustrative case reports. Because it is the only paper that presents a series of hypocalcemic patients, it is regularly cited in reviews on seizures caused by electrolyte disturbances (6, 7) and is part of the 'scientific backbone' for the association seizures and hypocalcemia. We suggest that the picture is more complex because we found, in a larger series of patients, that neurological complications could also be accounted for by perfectly valid alternative diagnosis such as alcohol withdrawal, space occupying lesions or cerebrovascular disease.

Other studies have focused on specific subgroups of hypocalcemic patients, in particular those with hypoparathyroidism (post-surgical and or idiopathic) (23, 24, 25, 26) and vitamin D deficiency (18, 27, 28). The prevalence of seizures in patients with hypoparathyroidism ranges from 30 to 70% (23, 24, 25, 26). These figures are much higher than ours but comparison is difficult for two reasons. Firstly, we describe an incidence of seizures presenting to the ED and not a prevalence of seizures in the study population. The prevalence in our population was still much lower at 10%. Reviews on seizures and electrolyte disturbances often do not properly differentiate incidence and prevalence (6, 7). Secondly, important confounding factors that could induce seizures such as hypomagnesemia, dysnatremia, once again are not reported. The higher prevalence of seizures in hypoparathyroidism could be related to the fact that the condition often goes undiagnosed for years, even in post-surgical cases, leading to intracerebral calcium deposits and epilepsy (25). The incidence of seizures in patients with vitamin D deficiency was close to ours and is reported as ranging from <5 to 16% (18, 27, 28). These studies concerned almost exclusively young children and neonates.

We found an in-hospital mortality of 18%, which increased to 35% if one only considers the patients with life-threatening cardiac or neurological complications. The causes of death were mainly uncontrolled cardiovascular disease and sepsis leading to multiple organ dysfunction syndrome. Whether calcium levels and mortality are

associated is still a major cause of debate. Reports have found conflicting results with either no association of calcium levels with mortality or both high and low levels of Ca reported to be associated with an increase in mortality (1, 2, 3, 4, 29). Sauter *et al.* studied unselected patients admitted to the ED and found that both hypocalcemia and hypercalcemia were associated with increased 28-day in-hospital mortality (1). Egi *et al.* found similar results in patients admitted to ICU (3). In contrast Steele *et al.* found no association between hypocalcemia on admission to ICU and mortality (4). Many consider that severely hypocalcemic patients simply represent a more severely ill subset of patients (4). Indeed correction of hypocalcemia in these patients was not associated with improved mortality (4, 30).

Limits

The first limitation is the retrospective nature of our study, which meant that certain aspects could not be properly assessed, for example the presence of Trousseau's and Chvostek's signs, paresthesia and psychiatric disturbances.

Secondly, even though it is ionized calcium that is physiologically active and under homeostatic control only few patients had ionized Ca determined on arrival at the ED, mostly because hypocalcemia was not initially suspected. We used the surrogate protein-corrected calcium. However, protein and albumin calcium adjustments have been criticized and are considered as poor predictors of ionized Ca, especially in patients with complex diseases or in acute settings (4, 31, 32, 33).

Third, the precise cause of hypocalcemia could not always be determined for two reasons.

1. A full biological work-up including magnesium, PTH and Vitamin D was not always available.
2. Some patients had multiple deficiencies, making the interpretation of PTH levels extremely difficult. This was the case for the 36 (27.1%) patients with hypomagnesemia. Indeed, many of these patients had associated vitamin D deficiency. The diagnosis of hypomagnesemia-induced hypoparathyroidism required a PTH level <50 nm/L, which was virtually never the case because the associated vitamin D deficiency would tend to increase PTH levels. Overall such patients would often have normal range PTH levels. We strictly applied diagnostic criteria for hypoparathyroidism and in doing so only found one case of hypomagnesemia-related hypoparathyroidism. Desai *et al.* found that a third of ICU patients had hypomagnesemia-related

hypocalcemia (29). His result however requires caution because PTH levels were not reported and he found no cases of vitamin D deficiency, which is classically one of the most frequent causes of hypocalcemia (9). Caution is also warranted for Gupta's study because he found that none of his 81 hypocalcemic patients had multiple causes of hypocalcemia and none had unexplained hypocalcemia implying that every patient had a complete work-up during the seventies and eighties, with PTH, vitamin D, magnesium and creatinine levels measured.

In conclusion, 13% of patients with severe hypocalcemia presented a life-threatening cardiac or neurological complication on the ED. However, in every case, a perfectly valid alternative cause could account for these complications. Further research is warranted to define the precise role of hypocalcemia and in particular its effect on patients with no underlying co-morbidities. A larger, prospective study is needed to definitely answer the question is severe hypocalcemia immediately life threatening?

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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