CASE REPORT

Hypocalcaemia in an adult: the importance of not overlooking the cause

Catarina Abrantes,¹ Daniela Brigas,² Hugo Jorge Casimiro,^{2,3} Margarida Madeira²¹Department of Nephrology, Setúbal Hospital Center, Setúbal, Portugal²Department of Internal Medicine, Setúbal Hospital Center, Setúbal, Portugal³Histology and Developmental Biology Institute, Faculty of Medicine, University of Lisbon, Lisboa, Portugal**Correspondence to**

Dr Hugo Jorge Casimiro, hugojorgecasimiro@gmail.com

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SUMMARY

A 58-year-old male patient was admitted at the São Bernardos's Hospital (Setúbal, Portugal) with generalised muscle spasms, dyspnoea, laryngospasm and bronchospasm in the context of severe hypocalcaemia. Despite efforts to correct serum calcium, it remained below average, leading to question the true cause of hypocalcaemia. Low parathyroid hormone and 25-hydroxyvitamin D, along with facial anomalies, palate defect and cognitive impairment with concomitant psychiatric disorder led to a suspicion of a DiGeorge/velocardiofacial/22q11.2 deletion syndrome (DS), which was confirmed through genetic testing. The 22q11.2 DS has a wide phenotypic expression and there are growing reports of diagnosis being made in adulthood. This case report highlights the importance of understanding the cause of refractory hypocalcaemia and alerts medical community to carefully access these patients, for this metabolic disorder may only present in later stages of life.

BACKGROUND

Hypocalcaemia is an electrolyte condition commonly detected in medical services and can result from a wide array of disorders. It may present from an asymptomatic laboratory finding to a severe, life-threatening situation, where immediate treatment is necessary.^{1,2}

Herein, we describe the case of a 58-year-old male patient admitted at our emergency department with signs of tetany following severe hypocalcaemia, refractory to corrective measures, which led to question its true cause.

After thorough clinical observation, and revisiting the patient's medical history, along with the findings of low-serum parathyroid hormone (PTH), velofacial dysfunction, dysmorphic features as well as cognitive impairment and a previous known psychiatric disorder, genetic testing for 22q11.2 deletion syndrome (22q11.2 DS) was performed which confirmed the diagnosis.

The 22q11.2 DS is one of the most common chromosomal disorders, affecting 1 in 3000–6000 newborns, according to the latest research.³ Almost 90% of patients have de novo or novel deletions caused by a random occurrence during fetal growth but autosomal dominant inheritance is also reported.^{3,4} As a result, there is a failure in the development of the derivatives of the various pharyngeal arches and pouches. There are a range of features associated with this syndrome, including congenital

heart disease, palatal abnormalities, dysmorphic facial findings, immune deficiency, developmental delay, intellectual disability and comorbid psychiatric disorders. Phenotypic expression is much more variable and extensive than previously recognised, however, and there is growing evidence of cases lacking some of the syndrome's pathological hallmarks, including cardiac or typical dysmorphic anomalies,^{5–9} leading to lower rates of clinical recognition.

With this case report we hope to enhance the need for careful evaluation of patients presenting with persistent hypocalcaemia, keeping in mind the medical, social and family histories.

CASE PRESENTATION

A 58-year-old male patient was admitted at the São Bernardo Hospital's emergency room (Setúbal, Portugal) with dyspnoea and signs of tetany. He had been assessed 1 week earlier at another clinic due to a 10-day history of productive cough and fever (maximum 39°C) and was diagnosed with a respiratory tract infection and treated with an antibiotic and glucocorticoid, without any improvement.

On arrival, the patient was alert, afebrile (36.4°C), with an increased respiratory rate (34 cycles per minute), along with facial cyanosis, severe hypoxaemia (blood oxygen saturation (Spo₂) 80% with fractional inspired oxygen (Fio₂) 21%), stridor and pulmonary wheezing. Muscle stiffness, involuntary muscle spasms and carpopedal spasm were noted. Cardiac and abdominal examinations were normal, and there were no signs of haemodynamic instability (124/78 mmHg, 87 bpm and regular).

Despite the overall presentation, an initial diagnosis of bacterial pneumonia was made following elevated inflammatory parameters (table 1, column 1) and a chest X-ray confirming a focal heterogeneous opacity in the left lower lobe associated with a parapneumonic pleural effusion. Inaugural kidney dysfunction AKIN III was also identified (table 1, column 1). Severely diminished ionised calcium on arterial gasometry (0.52 mmol/L) and prolonged QT interval (QTc 583 ms) on the ECG (figure 1) were initially overlooked although the results were accessible to the medical staff. The patient was then transferred to medicine department's wards under intravenous antibiotic, bronchodilator therapy and oxygen supplementation (Fio₂ 31%).

INVESTIGATIONS

Seventy-two hours after hospital admission, neuromuscular and respiratory symptoms worsened.

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Table 1 Biochemical data on admission, during hospitalisation and at discharge

	On admission	Day 3	Day 7	At discharge	Reference values
Haemoglobin (g/dL)	9.8	10.7	10.9	11.2	13–17
Haematocrit (%)	30	33	35	36	40–50
Platelet ($10^9/L$)	102	94	120	175	150–350
WCC ($10^9/L$)	12.2	15.5	9.8	5.2	4.5–11.4
Sodium (mEq/L)	139	144	142	143	136–146
Potassium (mEq/L)	5.1	5.0	4.1	4.2	3.5–5.1
Chloride (mEq/L)	103	103	102	103	98–107
Phosphorus (mg/dL)		10.5	6.2	5.7	2.7–4.5
Serum calcium* (mg/dL)		5.12	7.9	8.0	8.4–10.2
Ionised calcium (mmol/L)	0.52	0.6	0.7	0.9	1.15–1.32
Magnesium (mg/dL)		1.6	1.6	1.7	1.6–2.6
Urea (mg/dL)	124	171	156	39	18–55
Creatinine (mg/dL)	3.01	1.40	1.28	0.84	0.7–1.25
Glucose (mg/dL)	215	170	145	120	70–105
Albumin (g/dL)		2.1	2.3	2.5	3.5–5.0
CK (U/L)	626	300	82	34	30–200
25(OH)D (ng/mL)			8.5		>20
PTH intact (pg/mL)			14.4	12	15.0–68.3
TSH (μ U/mL)			4.03		0.35–4.94
ft4 (ng/mL)			0.45		0.70–1.48
CRP (mg/dL)	42	9.6	6.35	1.2	<0.5
ESR (mm/hour)			30		<30

*Corrected for albumin calcium levels.

25(OH)D, 25-hydroxyvitamin D; CK, creatine kinase; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; ft4, free thyroxine hormone; PTH intact, intact parathyroid hormone; TSH, thyroid-stimulating hormone; WCC, white cell count.

Analytic work-up and arterial gasometry were repeated (table 1, column 2), supporting the previous results, with severe reduction in ionised calcium and hypocalcaemia (5.12 mg/dL after correction for hypoalbuminaemia). Correction with intravenous calcium gluconate and oral calcitriol were started, with significant clinical improvement, mainly with cessation of tetanism and respiratory relief. QT normalisation was also observed. After completion of the antibiotic course, full resolution of the respiratory symptoms was observed and biochemical profile returned to normal, although serum calcium remained low, leading to question once again the true cause of hypocalcaemia, up to this point interpreted as part of the septic process.

Figure 1 Admission ECG revealing a prolonged QT interval (QTc 583 ms) and inverted T waves from V3 to V6, I and aVL.

Figure 2 Elongated face with a prominent forehead, a button-shaped nose and thin hair with alopecia areas visible at physical examination.

There were no previous relevant records regarding the patient's medical history, except being followed up at the psychiatric department for recurrent episodes of heteroaggressiveness, lacking a clear diagnosis. The patient had developmental delay with learning disability and uncharacterised cognitive impairment and was unable to complete general education. His family was from a rural community and lacking differentiation. His younger brother had died of unknown cause before completing 1 year of age; on his mother's side, there was a first-degree aunt institutionalised since childhood in a psychiatric institution (medical records could not be accessed) and a first-degree cousin with similar features and intellectual deficit as our patient.

His physical examination was also remarkable for an elongated face with a prominent forehead and a bulbous nasal tip, an absent palatine uvula with an hypernasal speech, thin hair with alopecia areas, hypopigmented skin areas and a micropenis that had not come to medical attention before (figures 2 and 3).

Additional laboratory data showed serum intact PTH in the lower limit of normal and low 25-hydroxyvitamin D which suggested primary hypoparathyroidism (table 1, column 3). The patient was unable to collect a 24-hour urinary sample. Kidney function returned to normal and renal ultrasound did not show any abnormality. Potassium, sodium and magnesium were within the reference values. Further endocrine studies found a reduced homogeneous thyroid gland in ultrasound with normal thyroid-stimulating hormone serum values and reduced free thyroxine hormone. Parathyroid scintigraphy revealed no anomaly. There was no history of thyroid surgery, neck trauma or radiation. Antithyroid autoantibodies were negative. Ocular examination revealed bilateral cataracts and audiological examination revealed moderate conductive hearing loss. Transthoracic echocardiogram showed no signs of congenital cardiac anomalies.

The major findings (hypoparathyroidism with concomitant hypocalcaemia, mental retardation, psychiatric disorder, facial dysmorphism and palate defect) guided our suspicion towards the 22q.11.2 DS, despite there was no evidence of other classical clinical characteristics (eg, congenital cardiac anomaly). A blood

Figure 3 Absence of palatine uvula.

sample was then submitted to an array-CGH 180K analysis, which identified a deletion in the long arm of chromosome 22 involving several genes, arr 22q11.21 (18 651 614–21 464 119) x1, confirming the diagnosis of 22q11.2 DS.

TREATMENT

After initial vigorous reposition with intravenous calcium gluconate, stable calcium levels were maintained with an oral association of calcium carbonate 1500 mg and cholecalciferol 400 IU two times daily.

OUTCOME AND FOLLOW-UP

After 4 weeks of hospitalisation, the patient was discharged with serum calcium of approximately 8 mg/dL and ionised calcium of 0.9 mmol/L (table 1, column 4). He attends regularly to our outpatient consultation, when his calcium levels are checked (on average between 6 mg/dL and 8 mg/dL), and there has been frequent need for intravenous correction. Eight months after hospital discharge, the patient was readmitted due to a new respiratory infection. Fertile first-degree relatives received genetic counselling. Despite our best efforts, we could not prove the existence of an autosomal dominant form of 22q11.2 DS in this family.

DISCUSSION

Hypoparathyroidism in 22q11.2 DS is caused by agenesis or hypoplasia of the parathyroid glands and occurs in the majority of patients.¹⁰ Hypocalcaemia is an expected result of hypoparathyroidism and frequently manifests during the neonatal period;

however, Cheung *et al*¹¹ showed that, in about 65% of patients, hypocalcaemia was first diagnosed in adulthood.

Hypocalcaemia itself may be of variable severity but in most cases of latent hypoparathyroidism PTH is secreted in sufficient amount to enable a stable value of serum calcium. In acute situations that increase calcium demand, however, PTH secretion is inadequate and symptomatic hypocalcaemia may occur. The onset and severity of hypocalcaemia is apparently affected by a multitude of mechanisms, including surgery, infection or trauma for example.¹² In the present case, severe hypocalcaemia was the main clinical presentation at admission, probably secondary to concomitant respiratory infection that worsened previous steady and asymptomatic hypocalcaemia. The presence of bilateral cataracts and moderate hearing loss may be an additional evidence for a long standing hypocalcaemia. CT scan of the brain did not show cerebral calcifications, also a relatively common consequence of chronic hypoparathyroidism.

Immunodeficiency is common in patients with 22q11.2 DS, particularly recurrent sinopulmonary infections.^{3 4 13} Our patient was admitted with a documented bacterial pneumonia and despite not having previous reports of recurrent infections, he was later hospitalised for a new pulmonary infection. In retrospective, the respiratory index event for which the patient was first admitted may have confounded medical staff to focus their attention towards the respiratory infection and initially undervalue the severe manifestations of hypocalcaemia, further delaying the diagnosis.

The present case is also impressive for establishing a 22q11.2 DS diagnosis in a 58-year-old man. To our best knowledge, there are only 4 reports of this genetic disorder at this age or older. This finding endorses the crescent number of published articles about 22q11.2 DS in adulthood. The reasons for these late diagnoses remain unclear, but there are several possible explanations. As stated before, 22q11.2 DS has a wide phenotypic spectrum and interindividual variance may hamper clinical suspicion. Moreover, patients that do not show some components of 22q11.2 DS, as is the case with congenital heart disease, tend to survive longer. Cardiac defects are among the most prevalent clinical manifestations, particularly conotruncal malformations (tetralogy of Fallot, interrupted aortic arch, ventricular septal defect and truncus arteriosus).¹⁴ After an exhaustive work-up we were unable to find any cardiopathy in our patient. Additionally, different ages and life stages may influence and alter the disease's presentation. For instance, facial features of 22q11.2 DS often become less pronounced with age. Subtle facial dysmorphic findings can be overlooked if the clinician is not well acquainted

Learning points

- ▶ The 22q11.2 deletion syndrome (DS) should be considered in the differential diagnosis of refractory hypocalcaemia due to primary hypoparathyroidism at all ages.
- ▶ Patients with chromosome 22q11.2 DS do not always show all components associated with this syndrome.
- ▶ Symptomatic hypocalcaemia associated with mental and behavioural disorders may be the clinical presentation of 22q11.2 DS in adulthood.
- ▶ Adults with 22q11.2 DS may be seen in virtually any medical practice due to the highly variable clinical characteristics and associated burden of morbidities.
- ▶ The diagnosis of 22q11.2 DS has clinical implications not only for affected adults but also for family planning as well.

with them and it may account for a delayed diagnosis.³ Likewise, psychiatric issues are more likely to develop with increasing age.¹⁵ Our patient had been followed for many years at the psychiatric department for recurrent episodes of heteroaggressiveness and mild cognitive impairment.

In conclusion, refractory hypocalcaemia due to primary hypoparathyroidism in adults is a rare disorder and being among the main features of 22q.11.2 DS and a potentially life-threatening manifestation should be considered in the differential diagnosis of 22q.11.2 DS. This case report emphasises the need for population-based prospective studies on adults with 22q.11.2 DS to better define characteristics and assist with clinical management.

Contributors CA was responsible for the overall content, including planning, conduct and reporting of the work. DB and MM was responsible for the conduct of the work, including literature search and data collection. HJC was responsible for conduct and reporting of the work.

Competing interests None declared.

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