



Hypocalcemia due to 22q11.2 deletion syndrome diagnosed in adulthood

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Summary

Chromosome 22q11.2 deletion syndrome (22q11.2DS) is a genetic syndrome that may present with hypocalcemia due to primary hypoparathyroidism (PH) at any age. We report a new diagnosis of 22q11.2DS in a 57-year-old man who presented with symptomatic hypocalcemia. It is important to consider genetic causes of hypocalcemia due to PH regardless of age.

Learning points:

- It is important to discard genetic cause of primary hypoparathyroidism in a patient without autoimmune disease or prior neck surgery.
- A new diagnosis of a hereditary disease has familial implications and needs genetic counselling.
- It is also important to discard other syndrome's comorbidities.

Background

Chromosome 22q11.2 deletion syndrome (22q11.2DS) is a genetic syndrome that may present with hypocalcemia due to primary hypoparathyroidism (PH) at any age.. Here we report the presentation and diagnosis of this rare genetic disease.

Case presentation

We report a 57-year-old man who presented with symptomatic hypocalcemia (perioral and finger numbness) during the postoperative period of a left nephrectomy for clear-cell carcinoma. He had a previous history of hypertension, hypercholesterolemia and type 2 diabetes. He was taking metformin, linagliptin, insulin glargine, simvastatin, enalapril and hydrochlorothiazide. He had no history of cervical surgery or autoimmune diseases but reported repeated episodes of bronchitis, learning difficulties and hypocalcemia in childhood. No data of growth were reported. Etiology of hypocalcemia

was not clarified but did require treatment with oral calcium supplements. Family history was unremarkable.

Investigation

On examination, some dysmorphic facial features stood out: a bulbous nose, small mouth and low-set ears. Trousseau's sign was positive. His weight was 79 kg, height 1.62 m and body mass index 30.1 kg/m². Behavioral disturbance and difficulty understanding medical recommendations was also observed. QT interval was normal in electrocardiogram (0.4 s). Laboratory tests showed hypocalcemia with a calcium level of 5.9 mg/dL (normal range, 8.4–10.2); ionized calcium, 3 mg/dL (4.6–5.28); albumin, 29.7 g/L (30–50); mild hypomagnesemia with a magnesium level of 1.59 mg/dL (1.6–2.6); and a normal phosphate level). Serum PTH and vitamin D levels were low: PTH, 11 pg/mL (15–88); 25-OH-vitamin D, 16 pg/mL (>30) and 1.25-OH-vitamin



D, 20 pg/mL (26–95). TSH was normal and TPO antibodies were negative. According to laboratory findings, hypocalcemia secondary to PH was diagnosed.

Treatment

Treatment with intravenous calcium, oral magnesium and oral calcitriol was initiated. After normalization of calcium and magnesium levels, he was changed to oral calcium. He was discharged with 500 mg of oral calcium three times a day and 0.5 µg of oral calcitriol once a day.

Outcome and follow-up

A genetic etiology was suspected due to PH, facial abnormalities and a history of hypocalcemia and bronchitis in childhood. Genetic testing with multiplex ligation-dependent probe amplification (MLPA) showed deletion of 3 Mb between LCR22A and LCR22D, compatible with chromosome 22q11.2 deletion syndrome (22q11.2DS). An echocardiogram showed that systolic function was normal and ruled out cardiac abnormalities. An immunological study indicated a mild decrease in CD4 and CD8 lymphocytes, with a normal proliferative response, advising vaccination against pneumococcus and *Haemophilus influenzae*. Nasopharyngeal exploration did not reveal velopharyngeal insufficiency. Bone densitometry (DXA scan) was normal (+2.9 lumbar spine *T*-score and –0.1 femoral neck *T*-score).

Discussion

22q11.2DS is a genetic syndrome that includes DiGeorge syndrome, velocardiofacial syndrome, conotruncal-facial syndrome and Cayler cardiofacial syndrome. It has an estimated prevalence of 1 in every 4000 live newborns. It is caused by a microdeletion of chromosome 22q11.2. Most deletions are de novo, with 10% inherited in an autosomal dominant pattern (1, 2).

Phenotypic features are variable, even within the same family. Most common clinical features include congenital cardiac defects, velopharyngeal insufficiency, facial anomalies, immune deficiency, hypocalcemia due to PH, learning difficulties and psychiatric disorders (3).

It is usually diagnosed in newborns or children, but diagnosis can be delayed to adulthood due to variability in type and severity of clinical manifestations.

Up to 13% of patients are diagnosed at age 15 years or older, most of them in the context of familial genetic

studies. Hypocalcemia secondary to PH might be the main reason for suspecting the disorder in adulthood. The main phenotypic features in adults are developmental delays with psychiatric and cardiac anomalies. It might increase the risk of early-onset Parkinson's disease (4).

Most patients present with hypocalcemia (49–80%), which can occur at any age (1, 2, 5, 6). Hypocalcemia is caused by PH due to congenital parathyroid aplasia or hypoplasia. PTH levels tend to decrease with age. PH can be transient, as in neonatal period; latent, manifesting in stressful situations such as infection, pregnancy or surgery or permanent (7). Apart from a low reserve of PTH due to parathyroid disease, hypomagnesemia also contributes to clinical hypocalcemia by blocking PTH secretion. In these cases, magnesium supplementation helps to minimize the risk of hypocalcemia (2). Our patient was treated with hydrochlorothiazide before surgery, which could have contributed to normalize calcium levels. In our case, hypocalcemia showed after surgery (stressing factor), and hypomagnesemia and the withdrawal of hydrochlorothiazide act as adjuvant factors. Hypocalcemia is treated with calcium and vitamin D analogues (calcitriol). It is recommended to maintain calcium serum levels at the lower limit of the normal range to avoid hypercalcemia, hypercalciuria, nephrolithiasis, nephrocalcinosis and renal insufficiency.

10% of patients with 22q11.2DS have autoimmune diseases such as autoimmune thyroid disease (which can appear in 30% of adults), celiac disease, atrophic gastritis, autoimmune thrombocytopenia and arthritis. Thus, annual thyroid function screening is recommended (7).

Our patient had renal carcinoma. Some cases of 22q11.2DS with neoplastic diseases have been published (hepatoblastoma, lymphoma, leukemia, neuroblastoma, renal carcinoma and thyroid carcinoma), suggesting augmented risk, probably due to immunodeficiency, chronic inflammation secondary to recurrent infections and functional alterations of catechol-O-methyltransferase (COMT). Since only 10% of cases with neoplasms described are adults, no specific recommendations for screening neoplastic diseases have been published (8, 9).

Other cases diagnosed in adulthood have been published (23–43 years), but our case is one of the oldest at diagnosis to be described (9, 10).

Declaration of interest

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



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Patient consent

Written consent has been obtained from the patient for publication of the submitted article.

Author contribution statement

Guillermo Serra is the physician of the patient. Maria Cabrer contributed to management of the patient and has permission of the responsible physician. Vicente Pereg and Maria Soledad Gogorza work in the same department as the main physician and discussed the diagnosis.

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