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DiGeorge syndrome with mild episodic hypocalcemia

Síndrome de DiGeorge con hipocalcemia transitoria leve

DiGeorge syndrome occurs in one out of every 4,000 to 9,700 live births^{1,2}. The genetic defect responsible has been found to be deletion in the 22q11.2 region, and the condition is thus currently included in the group of disorders of the 22q11 deletion syndrome. Cardiac malformations, immunodeficiency, hypocalcemia, palate malformations with velopharyngeal insufficiency, learning difficulties, and arrested development have mainly been reported. Genitourinary malformations, psychiatric disease, and bone and joint changes are less commonly found³. CATCH 22 (Cardiac defects, Abnormal facial features, Thymic hypoplasia, Cleft palate and Hypocalcemia) is the acronym used for these conditions.

We report the case of a 30-year-old female patient referred to the endocrinology outpatient clinic for low weight. Her personal history included surgery for patent ductus arteriosus at age 5 months, tremor with atypical myoclonic features, gothic palate, fracture of both kneecaps, lumbar scoliosis, hyperkyphosis and hyperlordosis, chondromalacia patella, rheumatic fibromyalgia, biphasic Raynaud's phenomenon, anemia and mild fluctuating thrombocytopenia, endometriosis, and adenoidectomy. She had no toxic habits and worked in a company for disabled people. Her family history included cases of malignant tumors, but no early deafness or blindness, nor known hereditary diseases. On direct questioning, the patient reported no rapid weight loss, recent changes in food intake, or incorrect feeding habits. She had previously stopped swimming because of weakness. There were no gastrointestinal symptoms, nor thyroid or adrenal symptoms. The patient denied excessive thirst. She had oligomenorrhea which had not improved after surgery for endometriosis or the use of oral contraceptives. The patient was concerned about her frequent respiratory infections. She experienced pneumonitis approximately three times per year, as documented by her primary care physician, with no prior choking. She had been prescribed valproate by the neurology department a few months before. The patient took ibuprofen daily for bone and joint

pain. The physical examination showed: weight, 43.5 kg; height, 163 cm; BMI, 16 kg/m². It also revealed the following: decreased muscle mass with preserved force; supine and sitting blood pressure values of 100/60 mmHg and 105/60 mmHg respectively; rhythmic pulse at 84 bpm; elongated face with microstomy; no oculomotor nerve paresis; no goiter palpated; no skin hyperpigmentation; normal cardiopulmonary auscultation; no abdominal masses palpated; no edema. Endocrinological work-up revealed normal results with regard to thyroid function, pituitary-adrenal axis, carbohydrate metabolism, and urinary catecholamine and metanephrine levels, with normal kidney and liver function. Laboratory tests showed no changes in standard nutritional parameters and trace elements. However, hypocalcemia (8.0 mg/dL, normal range, 8.6-10.2) with no associated hypoalbuminemia, normal phosphorus and decreased calcitriol levels (15 mcg/L, normal range 19-57) with no compensatory increase in parathormone levels (28 ng/L, normal levels 12-72) were found. Magnesium levels measured at the same time were also normal. Total 24-hour urine output was less than 1,000 mL on several occasions, and the calcium/creatinine ratio was estimated in fresh urine. In previous laboratory tests, calcium levels were almost always within the normal range, along with normal parathormone (Table 1), protein, and albumin levels. A review of the pediatric history confirmed recurrent pneumonitis since 15 months of age. A positive Mantoux test, positive cultures for *Giardia lamblia*, and common childhood viral infections were also found. Presumptive diagnoses were low weight with no proven endocrine etiology, mild vitamin D deficiency, and possible CATCH-22 syndrome. Adequate weight gain was achieved through customized dietary treatment. The genetics department confirmed the clinical suspicion and issued a diagnosis of 22q11.2 deletion syndrome. Abdominal ultrasound showed no urinary tract malformations. At the next visit, the patient had normal calcium levels without oral calcium or vitamin D supplementation and no changes in symptoms. Immunocompetence was assessed by the hematology department. We scheduled laboratory follow-up of phosphorus and calcium metabolism to start treatment based on calcium, phosphorus, calcitriol, and calcitriol levels and bone mineral density.

The patient was diagnosed at an uncommon age. Patients with DiGeorge syndrome are usually diagnosed in childhood based on the presence of congenital heart disease,

Table 1 Changes over time in phosphorus and calcium metabolism

Measurement	Normal values	February 2004	November 2006	July 2007	May 2008	November 2009	December 2009	June 2010
Calcemia (mg/dL)	8.6-10.2	8.4	9.1	8.8	—	8.9	8.0	9.4
Phosphoremia (mg/dL)	2.7-4.5	3.4	—	4.0	—	4.1	3.5	3.9
Calcidiol (mcg/L)	19-57	—	—	—	—	—	15	Inadequate sample
Calcitriol (pg/mL)	16-56	—	—	—	—	—	40	35
Parathormone (ng/L)	12-72	—	—	—	33	—	28	41
Ca/creat. ratio in fresh urine	< 0.14	—	—	—	—	—	19.92/225.61* =	26.7/189.02 =
Magnesium (mg/dL)	1.6-2.6	—	—	2.0	—	—	0.088	0.141

—: not requested; *: with pyuria.

symptomatic hypocalcemia, recurrent or unusual infections and/or a characteristic phenotype⁴. The reported patient was 30 years old, and her frequent episodes of pneumonitis, as well as the typical phenotype and surgery for ductus arteriosus called our attention from the very beginning. However, there was no established diagnosis of hypocalcemia. Respiratory infections could have been attributed to swallowing problems because of her facial malformation. The rest of her personal history made the discussed syndrome likely enough, or at the very least required that it should be ruled out.

As regards hypocalcemia, no prior or pediatric report had mentioned a potential correlation to her neurological symptoms. Moreover, her hypocalcemia was not consistent in all previously requested laboratory tests, as may occur in cases of partial or atypical expression of the syndrome. Based on this, it could be thought that she was one of the 40% of patients with no obvious calcium changes. The patient did not report clear paresthesia, her relative denied seizures in childhood, and before she was seen by us the neurology department had not issued a final diagnosis of her tremor. Neurological changes occur in 8% of cases, and hypocalcemia is assumed to be the causative agent in 68% of patients with epileptic seizures³. Our patient may therefore belong to the small group of subjects who experience neurological signs with an atypical expression at the times of transient hypocalcemia. Calcidiol deficiency was also found in previous tests, and the patient had been receiving valproate for some weeks and reported low weight. It could therefore have been thought that the main problem was nutritional in nature or related to vitamin D metabolism. However, when parathormone was measured in the presence of hypocalcemia, it was never found to be elevated in order to compensate for another change, which led us to suspect an at least partial primary parathyroid insufficiency.

Phenotypic expression probably becomes more atypical as the age at which this syndrome is suspected increases, because clinically unequivocal cases are diagnosed at an earlier age. It may be thought that the specialists who had previously seen our patient did not consider this diagnosis because of the unusual presentation of hypocalcemia. Suspicion should therefore be based on a few concordant classical signs and atypical features, as occurred in another previously reported case in which diagnosis was made at 15 years⁵. It is possible that if an early diagnosis had been made, our patient would have been monitored and treated for transient hypocalcemia, and bone and joint pain caused by her skeletal malformations would have been mitigated by rehabilitation therapy.

Heterogeneity has been reported in phenotypic expression of patients with the 22q11.2 deletion⁶. There appears to be no clear agreement on its nomenclature, as is shown by the multiple names it has been given. It is rather assumed that they are different expressions of the same disorder⁷. As a functional classification, we prefer the one that identifies patients with velo-cardio-facial syndrome as those who mainly have structural heart changes with facial dysmorphism, and patients with DiGeorge syndrome as those with thymic and parathyroid aplasia-hypoplasia. Our patient would therefore have a form which is intermediate between the two groups.

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Management of hypothyroidism secondary to tyrosine kinase inhibitors: description of treatment in three distinct clinical settings

Manejo del hipotiroidismo secundario a inhibidores de la tirosina quinasa: descripción del tratamiento en tres escenarios clínicos distintos

The pharmacological development of tyrosine kinase inhibitors (TKIs) is relatively recent, and TKIs are currently used as first or second line therapy for some solid and hematological tumors¹. Several studies have shown TKIs to be able to induce thyroid changes in 30% to 80% of treated patients depending on the series²⁻⁵.

The mechanisms proposed for the development of hypothyroidism during treatment with TKIs include thyroid atrophy induced by the drug either directly (cytotoxic versus autoimmune thyroiditis) or by inhibiting thyroid vascularization, the progressive depletion of thyroid reserves, and inhibition of iodine uptake.

Recommendations are available for the management of hypothyroidism induced by TKIs⁶, but none of them are based on scientific research, but rather on observations made in standard clinical practice and on retrospective studies. Three different clinical scenarios of TKI-induced hypothyroidism assessed in our outpatient clinics are reported.

Case 1

A 62-year-old female patient diagnosed with metastatic gastrointestinal stromal tumor (GIST). She was initially treated with imatinib (with no thyroid function impairment), but, due to therapeutic failure, this was switched to sunitinib 50 mg PO daily for 4 weeks with a 2 week rest (4-2 regimen). Laboratory tests during the third week of the fourth cycle showed subclinical hypothyroidism (TSH 7.90 µIU/mL, FT₄ 1.2 ng/dL, FT₃ 32 pg/mL) with negative antithyroid antibodies (ATAbs). The patient was therefore

referred to the endocrinology outpatient clinic for work-up. Since laboratory tests had been performed during the third week of the cycle, the tests were scheduled for the start and end of the following cycle. The results from laboratory tests performed on day 1 of the cycle after the 2 week rest period were normal (TSH 4.00 µIU/mL, FT₄ 1.4 ng/dL, FT₃ 3.9 pg/mL, negative ATAbs), and the results of tests performed on the last day of the cycle were consistent with asymptomatic subclinical hypothyroidism requiring no treatment (TSH 6.80 µIU/mL, FT₄ 1.4 ng/dL, FT₃ 3.6 pg/mL, negative ATAbs). The same occurred in the two subsequent cycles, and clinical observation with no replacement therapy was therefore decided upon.

Case 2

A 44-year-old female patient diagnosed with stage IV ectopic pleural thymoma. She was initially treated with sunitinib 50 mg PO daily (compassionate use) using a 4-2 regimen, which was reduced at the end of the third cycle due to a hypertensive crisis (her blood pressure was normal prior to treatment). No thyroid function tests were available before the end of the third cycle. At her first visit to the endocrinology outpatient clinic, laboratory test results performed at the end of the third cycle were consistent with subclinical hypothyroidism (TSH 12.80 µIU/mL, FT₄ 1.0 ng/dL, FT₃ 2.6 pg/mL) and ATAbs were negative. The patient was being treated with sunitinib 25 mg PO on alternate days (without rest) and enalapril 20 mg PO. She reported moderate to severe fatigue, in addition to non-quantified weight gain and cold intolerance. Treatment was started with levothyroxine (LT4) 125 mcg PO daily because she was on uninterrupted treatment and thyroid function could not therefore be assessed either at the start or end of the cycle. In the 12th week of treatment with LT4, the patient was found to have normal thyroid function (TSH 4.50 µIU/mL, FT₄ 1.4 ng/dL, FT₃ 3.0 pg/mL, negative ATAbs) and to show a significant improvement in fatigue symptoms. Replacement therapy was therefore continued.