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ABCD syndrome, an uncommon cause of hypercalcemia in pediatrics

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ABSTRACT

ABCD syndrome (ABnormal Calcium, Calcinosis, and Creatinine in Down syndrome) is characterized by an association of hypercalcemia, hypercalciuria, nephrocalcinosis, and impaired kidney function in patients with Down syndrome.

Only 7 cases have been published worldwide, although it is believed to be underdiagnosed. This report describes 2 new patients with ABCD syndrome and compares them with the cases reported to date.

Although it is a rare cause of pediatric hypercalcemia, it should be considered in children with Down syndrome once other more common etiologies have been ruled out. Once this diagnosis is confirmed, the recommended treatment is to reduce dietary calcium intake and work with an interdisciplinary team to maintain an adequate calorie and protein intake.

Keywords: *hypercalcemia; nephrocalcinosis; ABCD syndrome; Down syndrome.*

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INTRODUCTION

ABCD syndrome (ABnormal Calcium, Calcinosis, and Creatinine in Down syndrome) is characterized by an association of hypercalcemia, hypercalciuria, nephrocalcinosis, and impaired kidney function in patients with Down syndrome (DS), generally under 4 years of age.

It is an uncommon cause of hypercalcemia in pediatrics; only 7 cases have been published worldwide,[1] although it may be underdiagnosed.

ABCD syndrome is defined based on diagnostic criteria,[2] and the initial recommended treatment consists in hydration and a reduction in dietary calcium, although no long-term follow-up studies have been conducted.

The pathophysiological mechanism of ABCD syndrome may be associated with an increased intestinal calcium absorption. According to some authors, there may be an overexpression of transient receptor potential (TRP) channels that regulate this process, although the etiology is still not entirely clear.[2]

Here we describe 2 new patients with ABCD syndrome and compare them with the cases reported to date.

CASE REPORT 1

This was a 4-year-old male patient diagnosed with DS (karyotype 47, XY, +21), with no heart disease, and with a history of recurrent bronchial obstruction, post-viral lung disease, cord paralysis with tracheostomy and exclusive nasogastric tube feeding—through which he received 1500 mL/day of follow-on formula (1125 mg of calcium/day)—, who consulted the emergency department due to vomiting, diarrhea, and fever. He was in fair general condition with generalized pallor.

His laboratory tests showed mild leukopenia (4120 white blood cells/mL with 31% of neutrophils and 53% of lymphocytes), severe anemia (hemoglobin 5.4 g/dL), and normal platelets; impaired kidney function (creatinine 4 mg/dL, urea 94 mg/dL) with decreased glomerular filtration rate (GFR) (14 mL/min/1.73 ^{2}); normal pH, bicarbonate, sodium, potassium, and albumin levels; hypercalcemia (10.6 mg/dL), hyperphosphatemia (10.2 mg/dL), low parathyroid hormone (PTH) (4.7 pg/mL), normal vitamin 25(OH)D (47.4 ng/mL), and elevated urine calcium/creatinine ratio (0.8) in an isolated urine sample (*Table 1*).

A kidney ultrasound showed bilateral nephrocalcinosis (*Figure 1A*); a chest X-ray showed a normal cardiothoracic ratio (0.55); and the blood smear assessment conducted by the Department of Hematology was compatible with anemia of chronic disease, without atypical cells.

Volume expansion with saline solution and red blood cell transfusion were indicated; the patient was admitted to the hospital to complete diagnostic studies. Due to an increase in calcemia levels up to 11.8 mg/dL, 3 additional volume expansions with saline solution and furosemide were indicated; sevelamer carbonate, aluminum hydroxide, erythropoietin, and folic acid were added for the management of the chronic kidney

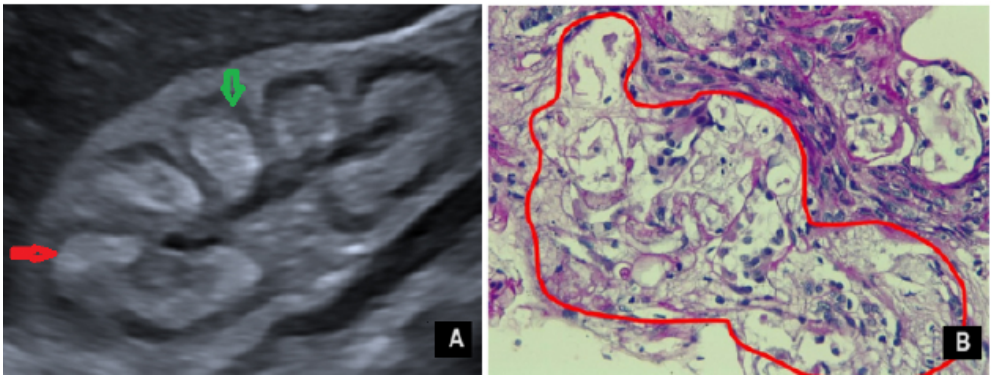
Table 1. Clinical and laboratory data

	Case 1	Case 2	Reference value
Age (years)	4	1.4	-
Weight (kg)	13.77	9	5–95
(Percentile for Down syndrome curves)	(50)	(25–50)	
Height (cm)	93	83	5–95
(Percentile for Down syndrome curves)	(75–90)	(95)	
Body mass index	15.9	13	-1 to +1
(Z-score)	(0)	(-3)	
Calcemia (mg/dL)	11.8	12.6	8.5–10.5
Ionized calcium correction (mmol/L)	1.34	1.52	1.18–1.27
Phosphatemia (mg/dL)	10.2	5.4	3.9–6
Creatininemia (mg/dL)	4	0.9	0.3–0.7
Uremia (mg/dL)	94	35	19–44
PTH (pg/mL)	4.7	16	12–95
Vitamin 25(OH)D (ng/mL)	47.4	49	20–50
Urine calcium/creatinine	0.8	0.8	0.2

PTH: parathyroid hormone.

1-25-dihydroxyvitamin D and parathyroid hormone-related peptide (PTHrP) were not measured because they were not available in our center.

Figure 1. Supplementary tests in relation to case report 1



A *Kidney ultrasound: both kidneys showed increased parenchymal echogenicity (red arrow) and scarce corticomedullary differentiation (green arrow), compatible with nephrocalcinosis.*
Size: the longitudinal diameter of the right kidney is 5.4 cm; the longitudinal diameter of the left kidney is 5.7 cm.
B *Pathological examination of kidney biopsy: the tubular compartment shows moderate atrophy and signs of tubular injury, with attenuation of the epithelium, loss of brush border, mononuclear and polynuclear tubulitis.*
The interstitium shows moderate fibrosis and diffuse lymphoplasmacytic-histiocytic inflammatory infiltrate with focal polynuclear leukocytes.
It is worth noting the finding of thick, bluish-purple, non-polarizing granular material linked to calcium phosphate, deposited in multiple foci, both in the tubular lumen and in the interstitium.
Final diagnosis: interstitial fibrosis/moderate tubular atrophy, with chronic active diffuse interstitial inflammation and microscopic nephrocalcinosis.

impairment.

In search of the etiological diagnosis, laboratory tests and imaging studies were performed, which ruled out cancer and granulomatous disease as causes of hypercalcemia; a kidney biopsy was compatible with nephrocalcinosis, with no signs of other underlying disease (*Figure 1B*).

ABCD syndrome was suspected, so water intake was increased and calcium intake was reduced; the initial response of calcemia levels was good and kidney function improved; and the patient was discharged from the hospital.

During the course of his condition, he was rehospitalized twice due to hypercalcemia (up to 13.7 mg/dL), for which he was started on methylprednisolone 1 mg/kg/day in order to inhibit 1 alpha-hydroxylation of vitamin D and decrease intestinal calcium absorption, but his response was inadequate.

The patient was assessed by a multidisciplinary team of the Departments of Nutrition and Feeding. Intake was progressively reduced using a formula with low calcium and phosphorus content and limited vitamin D content (RenaStart®), in association with an extensively hydrolyzed formula with added polimerosa and oil. Thus, it was possible to maintain an adequate calorie and protein intake with only 196 mg/day of elemental calcium. This was challenging because the formula had to be diluted to reduce the calcium, with the risk of not providing the recommended protein levels.

The videofluoroscopic swallowing study was normal, so the patient started progressive complementary feeding, with emphasis on food education. The extensively hydrolyzed formula was discontinued and creatininemia and calcemia levels remained stable and improved (1.2 mg/dL and 10 mg/dL, respectively).

The result of the kidney biopsy and the course of the patient's condition confirmed the presumptive diagnosis.

CASE REPORT 2

This was a male patient aged 1 year and 5 months diagnosed with DS (karyotype 47, XY, +21), with no heart disease, who consulted the pediatrics department due to poor weight gain and aversion to solid foods, so he was fed with 1000 mL/day of follow-on formula by suction (750 mg of calcium/day). He was in good general condition.

His laboratory tests showed normal hemogram; impaired kidney function (creatinine 0.9 mg/dL, urea 35 mg/dL) with decreased GFR (41 ml/min/1.73 m^2); normal pH, bicarbonate, sodium, potassium, and albumin levels; hypercalcemia (12.6 mg/dL); normal phosphatemia (5.4 mg/dL), low PTH (16 pg/mL); and normal vitamin 25(OH)D (49 ng/mL); and elevated urine calcium/creatinine

ratio (0.8) in an isolated urine sample (*Table 1*).

A kidney ultrasound showed bilateral nephrocalcinosis.

Given the experience with the previous patient, ABCD syndrome was initially suspected. The patient was hospitalized; formula and oral hydration were discontinued; his calcemia levels returned to normal to 9.9 mg/dL in 48 hours. When the patient started receiving again extensively hydrolyzed formula with elemental calcium intake of 200 mg/day, calcemia levels increased to 10.7 mg/dL, which confirmed the presumptive diagnosis. The patient was discharged with normal calcemia levels and improved kidney function, and promptly started receiving RenaStart® formula and speech therapy for retraining of the first stage of swallowing.

DISCUSSION

To define the etiological diagnosis of a patient with confirmed hypercalcemia, PTH levels should be assessed first to discriminate between dependent and independent causes. Among the independent causes, iatrogenesis caused by excess calcium intake or medications that can cause hypercalcemia are some of the most frequent causes in pediatrics, together with cancer and granulomatous disease. Genetic etiologies, either in isolation or as part of a syndrome, are rarer (*Figure 2*).

This report describes 2 children younger than 4 years old diagnosed with DS who presented with hypercalcemia, hypercalciuria, nephrocalcinosis, and impaired kidney function compatible with chronic kidney disease. In both cases, calcemia levels returned to normal and kidney function improved with the restriction of dietary calcium intake, as in the cases previously described. In our patients, this strategy was challenging for the treatment team because none of them consumed solid foods at the time of diagnosis (due to a swallowing disorder in the first case and aversion to solid foods in the second case). Both patients were receiving milk formula exclusively, which provided calcium above the recommended daily intake for their age of 500–700 mg. However, when adjusting the intake to this value, both patients persisted with hypercalcemia that only returned to normal once the intake was less than 200 mg/day, which confirmed an increase in intestinal calcium absorption, typical of ABCD syndrome. However, the pathophysiology of ABCD syndrome is still not clearly established.

When analyzing our patients together with the other reported cases (*Table 2*), we found no sex predominance; the median age at diagnosis was 18 months (range: 10–48); and the median calcemia levels was 13.2 mg/dL. All patients had bilateral nephrocalcinosis and, except for 1 patient, all of them had poor height and weight progression. Of the 6 patients who had recorded daily calcium intake, all exceeded the recommended daily intake.

In summary, ABCD syndrome is a rare

Figure 2. Diagnostic algorithm for hypercalcemia in pediatrics

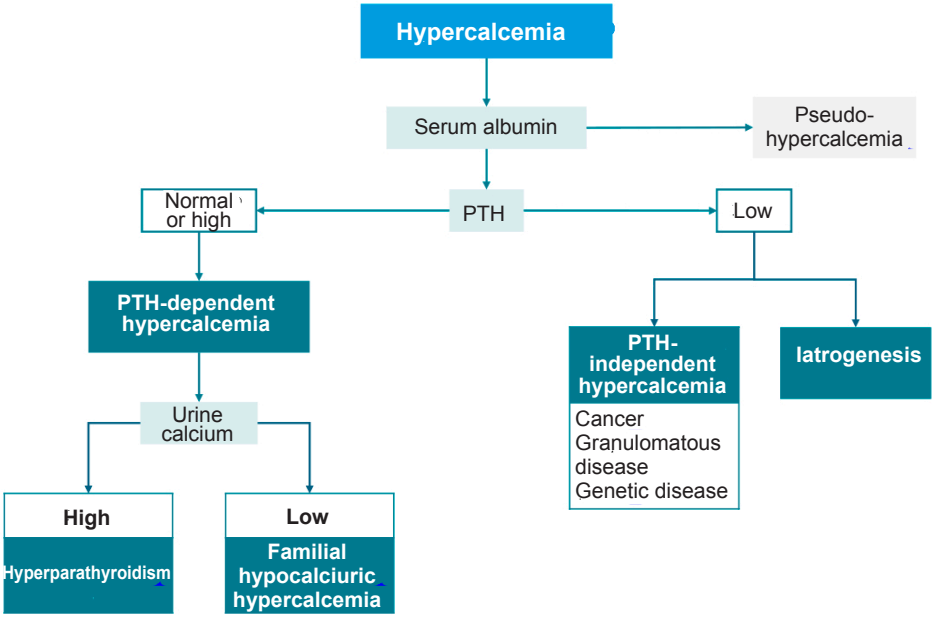


Table 2. Review of cases previously described and comparison with the patients included in this study

Case	Year and place	Age (months)	Sex	Reason for consultation	Maximum calcemia (mg/dL)	Creatininemia (mg/dL)	Urine calcium	Nephrocalcinosis (ultrasound)	Calcium intake (mg/day)
Proesmans et al.[3]	1995 Belgium	33	F	Poor height and weight progression	13	1.13	Ca/Cr 2.2	Bilateral	1200
Andreoli et al.[4]	1995 United States of America	18	F	Poor height and weight progression	14.4	1	Ca/Cr 1.1	Bilateral	-
Cobeñas et al.[5]	1998 Argentina	15	F	Poor height and weight progression	12	0.4	7 mg/kg/day	Bilateral	-
Filler et al.[6]	2001 Canada	10	F	Poor height and weight progression and vomiting	iCa (mmol/L)	0.69	Ca/Cr 2	Bilateral	650
Ramage et al.[7]	2002 United Kingdom	48	F	Laboratory finding	13.4	1.63	Ca/Cr 2	Bilateral	910
Tran et al.[2]	2009 Australia	24	M	Poor height and weight progression, constipation, and vomiting	12	0.51	Ca/Cr 1.8	Bilateral	700
Nguyen et al.[1]	2021 United States of America	11	M	Poor height and weight progression and vomiting	14	0.9	Ca/Cr 0.83	Bilateral	-
Case 1	2023 Argentina	48	M	Poor height and weight progression and vomiting	13.7	4	Ca/Cr 0.8	Bilateral	1125
Case 2	2023 Argentina	17	M	Poor height and weight progression	12.6	0.9	Ca/Cr 0.8	Bilateral	750

iCa: ionized calcium; Ca/Cr: urine calcium/creatinine ratio.

cause of pediatric hypercalcemia that should be considered in children with DS once other more common causes, such as iatrogenesis, cancer, and granulomatous disease, have been ruled out.

Once confirmed, the recommended treatment for ABCD syndrome is a reduction of dietary calcium. If it is not possible to discontinue the consumption of dairy products, the recommendation is to use special formulas for this population and have providers from the departments of nutrition and feeding work together on patient care to ensure an adequate calorie and protein intake.

In all pediatric patients who are exclusively fed with milk formulas, the following is recommended:

- Maintain calcium intake appropriate for age and clinical condition taking into account baseline disease, kidney function, growth, development, immobilization, and potential intercurrent conditions.
- Ensure an adequate hydration.
- Perform a phosphocalcic profile test and kidney ultrasound in patients with high calcium intake or symptoms compatible with hypercalcemia. ■

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