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## PEDIATRIC DIABETIC KETOACIDOSIS IN A PATIENT WITH DOWN SYNDROME. CASE REPORT

**Keywords:** Diabetic Ketoacidosis; Down syndrome; Type 1 Diabetes; Pediatrics.

**Palabras clave:** Cetoacidosis Diabética; Síndrome de Down; Diabetes Mellitus Tipo 1; Pediatría.

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## ABSTRACT

**Introduction:** Patients with Down syndrome (DS) have an increased risk of developing autoimmune diseases. This is a rare case of a pediatric patient with DS with an initial clinical profile of diabetic ketoacidosis.

**Case presentation:** 6-year-old male patient with symptoms suggestive of diabetes mellitus type 1 (DM1) of 15 days of evolution (polyuria, polydipsia, polyphagia and loss of 2 kilos of weight), who was admitted to the emergency department of the Hospital de San José, in Bogotá, Colombia, with uncontrollable vomiting and dehydration. The tests performed confirmed moderate ketoacidosis: glycometry: 592 mg/dL, pH: 7.19, HCO<sub>3</sub>: 10 mmol/L, PCO<sub>2</sub>: 45, PO<sub>2</sub>: 95 and lactic acid: 1.4 mmol/L. Management with isotonic fluids and intravenous insulin therapy was initiated and the patient was transferred to the pediatric intensive care unit, where ketoacidosis was controlled in approximately 10 hours. Subcutaneous insulin schedule was initiated without complications.

**Discussion:** This case highlights the importance of monitoring possible autoimmune complications in patients with DS, since the risk of developing them is 4.2 times higher than in the general population.

**Conclusion:** This case calls on to contemplate autoimmune complications in patients with DS during clinical practice. Although they are not part of the most frequent reasons for consultation, they cannot be underestimated and should be suspected and treated in a timely manner.

## RESUMEN

**Introducción.** Los pacientes con síndrome de Down (SD) tienen mayor riesgo de enfermedades autoinmunes. A continuación, se presenta un caso inusual de un paciente pediátrico con SD quien debuta con un cuadro de cetoacidosis diabética.

**Presentación del caso.** Paciente masculino de 6 años con síntomas sugestivos de diabetes mellitus (DM) tipo 1 de 15 días de evolución (poliuria, polidipsia, polifagia y pérdida de 2 kilos de peso), quien ingresa al servicio de urgencias del Hospital de San José, en Bogotá, Colombia, con vómito incoercible y deshidratación. Se realizan exámenes que confirman cuadro de cetoacidosis moderada, glucometría: 592 mg/dL, pH: 7.19, HCO<sub>3</sub>: 10 mmol/L, PCO<sub>2</sub>: 45, PO<sub>2</sub>: 95 y ácido láctico: 1.4 mmol/L. Se inicia manejo con líquidos isotónicos e insulino terapia endovenosa y se traslada a la unidad de cuidado intensivo pediátrico, donde se controla la cetoacidosis en un aproximado de 10 horas. Se da inicio de esquema de insulina subcutáneo sin complicaciones.

**Discusión.** Este caso resalta la importancia del seguimiento de posibles complicaciones autoinmunes en pacientes con SD, ya que el riesgo de estas es 4.2 veces mayor en población con SD.

**Conclusiones.** El presente caso invita a contemplar las complicaciones autoinmunes en pacientes con SD durante la práctica clínica. Si bien no hacen parte de los motivos de consulta más frecuentes, no se pueden subestimar, sino que deben sospecharse y tratarse oportunamente.

## INTRODUCTION

Patients with Down syndrome (DS) are at high risk of developing autoimmune diseases, including diabetes mellitus type 1 (DM1), one of the most common endocrine autoimmune diseases. The risk of presenting this type of disease is 4.2 times higher in patients with DS compared to the general population (prevalence of 0.38% in DS vs. 0.09% in the general population), with a peak incidence before 2 years of age and a second peak in early adolescence. (1)

Blood studies show a high frequency of glutamic acid decarboxylase (Anti-GAD) antibodies in patients with DS presenting with DM1; they are also associated with other autoimmune disorders, mainly thyroid and celiac disease. (2) This report presents the case of a patient with DS, with no history of thyroid or celiac disease with an initial clinical profile of diabetic ketoacidosis.

## CASE PRESENTATION

6-year-old male patient, from Puerto López (Meta, Colombia), mestizo, student, with a history of DS, who required endovascular closure of a patent ductus arteriosus 3 years before consultation; he also had a history of pneumonia at 6 months of age, which required in-hospital management. The mother reported continuous medical checkups and no abnormal events.

The patient visited the emergency department of the Hospital de San José, in Bogotá D.C., due to a clinical profile of 1 day evolution, consisting of 10 emetic episodes of food at first, which progressed to biliary content associated with generalized abdominal pain; he did not present with dysthermias, nor diarrheal episodes or respiratory symptoms. The patient's mother stated that he had presented other symptoms in the last 15 days such as

polyuria, polydipsia, polyphagia and loss of 2 kilos of weight.

Physical examination revealed a normocephalic eutrophic patient with flat nasal bridge, low-set ears and clinodactyly. Vital signs were: blood pressure: 94/79 mmHg, heart rate: 129 beat/min, respiratory rate: 26 breaths/min, temperature: 36.7°C, and pulse oximetry saturation: 92%. The only additional findings of importance were signs of dehydration (dry oral mucosa, tachycardia, and hypotension), drowsiness and soft abdomen without abdominal guarding. Glucometry reported values >592 mg/dL and venous blood gases that evidenced metabolic acidosis (pH: 7.19, HCO<sub>3</sub>: 10 mmol/L, PCO<sub>2</sub>: 45, PO<sub>2</sub>: 95, lactic acid: 1.4 mmol/L). No antibodies test was taken, since it is not a routine practice at the hospital.

The child presented with polyuria, polyphagia, polydipsia and weight loss suggestive of diabetes, in addition to laboratory tests that showed hyperglycemia and metabolic acidosis, symptoms compatible with a diagnosis of moderate diabetic ketoacidosis (DKA). He was transferred to resuscitation for monitoring, and intravenous isotonic fluids (bolus of 10 mL/kg) and insulin infusion (0.1 U/kg/hour) were initiated. Follow-up continued in the pediatric intensive care unit.

In the pediatric intensive care unit, insulin infusion was maintained and isotonic fluids were administered at 120 mL/hour (160 mL/kg/day) with 40 mEq/L of potassium chloride. Additional admission tests reported elevated urea nitrogen (BUN) (35mg/dL); high level of serum sodium at 150mEq/L; normal serum potassium (4.9 meq/L); elevated level of chlorine at 110 mEq/L, but adequate sodium level; total serum calcium (9.7mg/dL); phosphate of 7.5 mg/dL, unusually high for DKA; and glycosylated hemoglobin (HbA1c) at 8.17%, slightly elevated. These results confirmed the recent nature of the disease.

Furthermore, a partial urine test was performed, which did not suggest an infectious profile, although it showed the presence of ketones; consequently, no complete blood count was required. Other tests were taken, including thyroid hormone profile, TSH 0.4 mU/l and T4L 16.8 pmol/L, which were not suggestive of active concomitant thyroid disease. DKA correction was achieved 10 hours after initiating the treatment, with adequate clinical evolution; the scheme was switched to subcutaneous insulin with doses of 0.8 U/kg/day with 7 UI of insulin detemir and 2 UI of insulin aspart with each meal.

Multidisciplinary in-hospital management continued together with nutrition for input management and food education, physical activity and psychotherapy. DKA successfully resolved and no adverse reaction to the established treatment was observed during hospital stay.

## DISCUSSION

DS was first described in 1986 by J.L Down (1) and is considered the most common chromosomal aneuploidy and at the same time the main cause of cognitive retardation worldwide. In Colombia, it is in the fourth most common congenital malformation, more frequently found in male patients. (3) Its incidence is around 1/700 to 1/1500 live births, which increases with maternal age. 95% of cases are caused by nondysjunction in meiosis I. (4,5)

Compared to the general population, patients with DS have a significantly higher risk of developing DM1 and autoimmune thyroiditis, which is why multiple studies have been conducted to identify immune alterations. (5-8)

About 25% of DM1 cases present with an initial clinical profile of DKA. Children, especially those under the age of 5, are at high risk for DKA, and its severity is also inversely related

to the age at which it occurs, with a mortality rate of 0.15% to 0.3%. (9)

## Pathophysiology

DKA is a metabolic disorder caused by the absolute or relative deficit of insulin associated with a concomitant rise in counterregulatory hormones. Excess counterregulatory hormones and insulin deficit induce lipolysis, which in turn increases non-esterified fatty acids in the bloodstream. These acids are the base for ketogenesis and are transformed into Acyl-CoA; once they reach the mitochondria by means of carnitine, beta-oxidation takes place, transforming into Acetyl-CoA, which under normal conditions will be completely oxidized. However, many derivatives of acyl-CoA are observed in DKA, which saturate the pathway and are partially oxidized, giving rise to three  $\beta$ -hydroxybutyrate and acetoacetates known as ketone bodies. This is considered as the extreme manifestation of deterioration in carbohydrate metabolism. (10-13)

It has been demonstrated that patients with DS older than 5 years have excessive IgA and IgG, with high levels of IgG1 and IgG3, low levels of IgG2 and IgG4 and decreased levels of IgM, which would generate an exaggerated response with a marked decrease in the production of natural antigens that worsens from infancy to adulthood. (12-15)

Moreover, it is evident how genetic polymorphisms generate a reduced thymic output that targets insulin, the A chain of the acetylcholine receptor and the TSH receptor, in turn generating an alteration in the extracellular adenine nucleotides and nucleosides that participate in the regulation of inflammation by stimulating the pro-inflammatory pathway and the anti-inflammatory cytokines that contribute to immune deregulation in patients with DS. (2,13-15)

The genotype most frequently associated with DM1 in the general population is HLA class II DR4/DQ8/DR3-DQ2, which is also found in patients with DS, generating a common pathogenesis. (16) People with DS are usually treated with simple insulin regimens for better therapeutic adherence; this, added to a simple lifestyle and the acceptance of routine, leads to less complications. (17)

As has been shown, the clinic of DKA can be variable, overlooked and even mistaken for other pathologies. This was the case of a patient who attended periodic medical checkups during which no glycemic alterations had been observed, making this pathology more insidious. Cognitive delay in these patients is also a factor that contributes to the underestimation of the symptomatology. (18)

The symptoms of patients with DS presenting with DKA may manifest through hyperglycemia, polyuria, polydipsia, weight loss and dehydration; in addition, this clinical profile may lead to acidosis, vomiting, extreme thirst, tachycardia, hypotension, drowsiness and hyperventilation. In the presence of these symptoms, it is necessary to take into account the following diagnostic criteria to initiate a timely treatment. (19)

### Diagnostic criteria

Diagnostic criteria include glycemia  $>200$ - $250$  mg/dL, pH  $<7.3$ , bicarbonate  $<15$  mEq/L and ketonemia  $>3$  mmol or ketonuria.

Once DKA has been diagnosed, timely management should be initiated. Both in patients with DS and healthy patients, management is performed by starting with rehydration using isotonic solutions to restore the circulating volume and the glomerular filtration rate, and avoid cerebral edema. In case of shock or severe dehydration, boluses at 10 mL/kg may be used for an estimated time of 10 to 30 minutes

(19,20); this intervention should be carried out with caution due to the danger of worsening the risk of cerebral edema. Maintenance fluids should be supplied by calculating a deficit that is usually close to 10%. (19-22).

On the other hand, insulin therapy as treatment should be initiated in order to correct hyperglycemia, ketogenesis and glycogenolysis; to inhibit lipolysis; and to counteract excessive levels of counterregulatory hormones. Thus, a dose of 0.5 to 0.1 IU/kg/h will be started and corrected according to the glucometries. (9,23) These patients will benefit from continuous monitoring until acidosis is corrected.

### CONCLUSIONS

Patients with DS have significantly higher rates of developing autoimmune disorders than the general population. This chromosomal aneuploidy is considered a risk factor for the onset of DM1 and autoimmune thyroiditis; therefore, patients suffering from this syndrome should be monitored periodically. This should also be done to make early diagnoses, start early treatment, and decrease the occurrence of complications. These patients will have a better control of their disease given the simplicity of the indicated insulin schemes and their adherence, which reduces the presentation of complications compared to the general population.

This case report calls on to contemplate autoimmune complications in patients with DS during clinical practice, which should be suspected and treated in a timely manner. Although DM is a multifactorial and polygenic disease, hypothesis suggest that patients with DS have an alteration in the mutated chromosome 21 that predisposes them to have a higher rate of autoimmune diseases. This must be confirmed through genetic studies in larger populations.



## CONFLICT OF INTEREST

None stated by the authors.

## FUNDING

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