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CLINICAL CASE

Perinatal factors and type 1 diabetes-associated dysbiosis in Mexican infants

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KEYWORDS
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Abstract
Background: Type 1 diabetes (T1D) is currently an autoimmune disease occurring more frequently and early in life. T1D development requires genetic predisposition and environmental factors, which influence the gut microbiota in early infancy and could increase the risk for T1D-associated autoimmunity. In Mexico there are no published microbiota studies in children <6 years old with T1D.
Case reports: We report two contrasting Mexican T1D cases of children <6 years of age and a third case of a healthy child prior to autoimmunity and T1D onset. Perinatal factors, feeding regimes in the first year of life and gut microbiota composition are discussed and related to the T1D onset. The three cases show a particular microbiota profile with decreased bacterial diversity as compared with healthy children, which could be related to environmental factors prior to the development of T1D and disease control.
Conclusions: T1D infant cases presented a decreased bacterial diversity, which appeared before autoimmunity and T1D onset. Glycemic control could tend to correct the gut dysbiosis in T1D children. Prospective studies are needed to follow-up healthy children at high genetic risk to assess factors related to the microbiota structure.

PALABRAS CLAVE
Diabetes tipo 1;
Factores perinatales;
Lactancia materna;
Microbiota intestinal;
Reporte de casos;
México

Factores perinatales y disbiosis asociada con diabetes tipo 1 en niños mexicanos

Resumen
Introducción: La diabetes tipo 1 (DT1) es una enfermedad autoinmune que cada vez es más frecuente y se presenta a edades más tempranas. Su desarrollo requiere de predisposición genética y factores ambientales que influyen sobre la microbiota intestinal en la infancia

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temprana que pudieran aumentar el riesgo de autoinmunidad asociada con DT1. En México no existen publicaciones de estudios de microbiota en niños menores de 6 años con DT1.
Casos clínicos: Se reportan dos casos de DT1 contrastantes de niños mexicanos menores de 6 años de edad y un tercer caso de un niño sano, previo al desarrollo de autoinmunidad y DT1. Se discuten los factores perinatales, los regímenes de alimentación en el primer año de vida y la microbiota intestinal en relación con el desarrollo de DT1. Los tres casos presentaron una microbiota particular con disminución de la diversidad bacteriana en comparación con los niños sanos, lo cual pudiera estar relacionado con factores ambientales previos al desarrollo de la enfermedad y con el control de la DT1.
Conclusiones: Los niños con DT1 presentaron una diversidad bacteriana disminuida que aparece antes de la autoinmunidad y DT1. El control glucémico podría corregir la disbiosis intestinal en DT1. Faltan estudios prospectivos que den seguimiento a niños sanos con alto riesgo genético y evalúen factores relacionados con la estructura de la microbiota.

1. Introduction

Type 1 diabetes (T1D) is one of the most frequent autoimmune diseases in children with a prevalence of 1:300[1]. Advances in the study of predisposition factors during the last decade increase the evidence of an intestinal origin for T1D which, in turn, reveals an unexplored area for understanding the diabetes etiology. The interplay between early feeding patterns, infections and use of antibiotics during the first years of life has taken a central role because all influence the microbiota composition and gut permeability. Associations have been found in animal models of the interactions of these factors in relation to the development of T1D[2]. Although the first studies in children at high genetic risk have shown gut dysbiosis at the T1D onset, these changes are affected by diet, geography[3] and other factors such as age[4]. Furthermore, it is unknown whether these changes in microbiota are a cause or an effect of the characteristic metabolic disturbance of T1D.

We report a case series of two contrasting Mexican T1D patients (6 years old and younger) and a third case of a healthy child prior to autoimmunity and T1D onset, all recruited from the Children's Hospital of Sonora (HIES), Mexico. Elements of their diet in the first year of life and perinatal factors are discussed and related to the T1D diagnosis and the gut microbiota composition, assessed by pyrosequencing of the V4 region of the 16S rRNA gene following the methods described previously[5]. Microbiota data of the cases were processed and analyzed in the Quantitative Insights Into Microbial Ecology (QIIME) pipeline[6].

2. Case reports

2.1. Case 1

We present the case of a 6-year-old female with 3 days evolution of T1D diagnosed when she was hospitalized for diabetic ketoacidosis (glucose: 538 mg/dl). The patient was the product of a fifth pregnancy complicated with oligo-hydramnios and fetal distress. The mother was a passive smoker during pregnancy. The patient was born vaginally at 38 weeks of gestation and breastfed until 2 months of age. She had complementary milk formula since birth. At 6 months of age, wheat and other cereals were introduced into her diet. Since the first year, the child presented an average of six infections per year (respiratory and gastrointestinal) treated with antibiotics (amoxicillin, trimethoprim/sulfamethoxazole, and cephalexin). She suffered from acute tonsillitis 2 weeks prior to the diagnosis of T1D.

T1D-associated autoantibodies were as follows: positive to anti-glutamic acid decarboxylase (Anti-GAD) and anti-tyrosine phosphatase-like protein (Anti-IA2).

Risk phenotype was DRB1*04/DQA1*0301.

2.2. Case 2

This is the case of a 2-year-old female with T1D diagnosed 2.5 months before the study. She has had excellent adherence to treatment with insulin and diet. She was born by eutocic vaginal delivery without perinatal complications. She had a mixed feeding regimen with breast milk and formula from birth to 2 months old, continuing only with cow's milk formula. Wheat and other cereals were introduced into her diet when she was 2 months old. She suffered two respiratory and four gastrointestinal infections of unknown etiology during her first year of life. All diseases were treated with antibiotics (amoxicillin, trimethoprim/sulfamethoxazole). Current fasting glucose was reported as 105 mg/dl. T1D-associated autoantibodies were positive to Anti-IA2.

Risk phenotype was DRB1*03/DR4-DQ8.

2.3. Case 3

We present the case of a 6-year-old male who was healthy at the time of the study. His brother is a T1D patient. The patient is the term product of a second pregnancy born by cesarean due to cephalo-pelvic disproportion, without perinatal complications. He was breastfed for 3 months, continuing with cow's milk formula since that age until he was 1 year old. Cereals such as wheat were introduced to