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Kabuki syndrome associated with type 1 diabetes mellitus: report of three cases

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ABSTRACT

Kabuki syndrome is a rare genetic disorder characterized by distinctive facial features, intellectual disability, skeletal abnormalities, short stature, and dermatological disorders, among other clinical manifestations. There is an increased risk of associated autoimmune diseases (such as thrombocytopenic purpura, hemolytic anemia, vitiligo, and type 1 diabetes).

Type 1 diabetes is caused by autoimmune destruction of the beta cells of the pancreas and is the most common form of diabetes in children and adolescents.

We present three pediatric patients with a diagnosis of Kabuki syndrome and type 1 diabetes, two of whom have an associated second autoimmune disease.

Keywords: *Kabuki syndrome; type 1 diabetes mellitus; autoimmunity.*

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INTRODUCTION

Kabuki syndrome (KS) is a rare genetic disorder with an estimated prevalence of 1 in 32 000 live births and affects both sexes equally. The most common inheritance pattern is autosomal dominant due to mutations in the *KMT2D* gene, although most cases are sporadic, suggesting *de novo* mutations.[1]

There is a variant called Kabuki type II due to mutations in the *KDM6A* gene (Xp11.3) with an X-linked inheritance pattern.[1]

This syndrome is characterized by distinctive facial features (eversion of the outer third of the lower eyelid, arched and sparse eyebrows in the outer third, broad nasal bridge with depressed nasal tip and prominent ears), intellectual disability, skeletal abnormalities, short stature, and dermatologic alterations, among other clinical manifestations. The molecular basis of KS lies in pathogenic variants in the *KMT2D* and *KDM6A* genes encoding the enzymes lysine methyltransferase 2D and lysine demethylase 6A, respectively, which are part of a Set1-associated protein complex called COMPASS. This complex is involved in chromatin remodeling through epigenetic modification of histones and plays a crucial role in regulating gene expression.[2,3]

Association of KS with autoimmune diseases such as immune thrombocytopenic purpura (ITP), vitiligo, autoimmune thyroiditis, and type 1 diabetes *mellitus* (DM1) has been reported.[3]

DM1 is the most common form of diabetes in children and adolescents. It results from autoimmune destruction of the beta cells of the pancreas. There are five main types of antibodies (markers of autoimmunity) against pancreatic islets: insulin/proinsulin autoantibodies (IAA), anti-islet cell antibodies (ICA), 65 kDa glutamic acid anti-decarboxylase (GADA), anti-insulinoma antigen tyrosine phosphatase 2A (IA-2A) and anti-zinc transporter 8 (ZnT8A).[4] Its association with other autoimmune diseases is frequent; the most prevalent are Hashimoto's thyroiditis and celiac disease.[5]

The prevalence of diabetes in patients with KS is poorly documented.[3] The following paper aims to present three patients with a diagnosis of KS and DM1.

CLINICAL CASE 1

Male patient, 16 years old, diagnosed with KS (typical facial features, short stature, cleft palate, brachydactyly, clinodactyly of the fifth finger of both hands, persistence of the fetal pads of the thumb of the fingers, and intellectual disability), diabetic debut at 12 years of age with severe diabetic ketoacidosis. He presents positive ICA and GADA antibodies. He is on basal-bolus insulin treatment with adequate metabolic control, without complications or associated diseases.

CLINICAL CASE 2

Female patient, 18-year-old patient, diagnosed with KS (characteristic facial features, short stature, operated coarctation of the aorta, and intellectual disability), overweight (body mass index: 28.19, Z-score between +1 and +2), recent diagnosis of polyarticular juvenile idiopathic arthritis, in treatment with methotrexate and meprednisone 12.5 mg/day. She was referred to the Nutrition and Diabetes Department due to hyperglycemia. Glycemia of 310 mg/dl was found in the consultation. Laboratory tests: glycosylated hemoglobin 10.9%, C-peptide 1.68 ng/ml, and positive GADA and IAA antibodies. She started basal-bolus treatment with insulin with good evolution.

CLINICAL CASE 3

Female patient, 15-year-old, diagnosed with Hashimoto's thyroiditis, under treatment with levothyroxine since the age of 4 years, and a history of surgery for ocular malformation (eyelid eversion) and tonsillectomy. Diagnosis of Kabuki syndrome (characteristic dysmorphic features, persistence of fetal finger pads, brachydactyly, ogival palate, short stature, developmental delay, intellectual disability, and feeding difficulties). Diabetes onset at six years of age in chemical ketosis, for which she was referred to the Nutrition and Diabetes Department of our hospital. There is no antibody test for diabetes. She is treated with basal-bolus insulin with regular metabolic control. She was hospitalized twice for ketoacidosis; on one occasion, she was admitted to the intensive care unit and required mechanical ventilation. She evolved with subglottic stenosis and required tracheostomy (later closed). He needed treatment for peripheral neuropathy (with thioctic acid and gabapentin).

None of the patients have a genetic study for KS; the diagnosis is clinical and performed by a physician specializing in genetics.

DISCUSSION

KS is a rare genetic syndrome with significant heterogeneity in its clinical manifestations and multisystem involvement. In 2019, Adam et

al.[6] published an international consensus with diagnostic criteria for KS (*Table 1*).

Differential diagnoses include CHARGE, branchio-oto-renal, Ehlers-Danlos (hypermobile form), Hardikar syndromes, IRF6-linked disorders, and 22q11 microdeletion syndrome.[7]

Genetically, KS is caused by pathogenic variants in the *KMT2D* (70% of cases, with autosomal dominant inheritance, although most cases are de novo) and *KDM6A* (5% of cases, X-linked inheritance) genes. There is a percentage of patients with a clinical diagnosis of KS in whom the genetic cause is unknown. The *KMT2D* gene is located on chromosome 12 and encodes the enzyme lysine methyltransferase 2D, which acts as a histone methyltransferase. The *KDM6A* gene is located on chromosome X and encodes the lysine-specific demethylase 6A enzyme that acts as a histone demethylase. Both are part of the epigenetic machinery, which regulates gene expression during embryonic development and in various biological processes.[7,8] Monogenic alterations of epigenetic regulators affect many genes and cause multiple clinical manifestations and multisystem involvement.[9]

Among the clinical manifestations of KS, immunological alterations have been described, both an increased frequency of immunodeficiencies and autoimmune diseases; the most reported are ITP, hemolytic anemia, and, among the non-hematological ones, vitiligo.[2,8] The COMPASS complex participates in the epigenetic regulation of the *FOXP3* gene, which is fundamental in the development and function of regulatory T cells and is responsible for mediating the immune response and tolerance to autoantigens. Pathogenic variants in the *KMT2D* or *KDM6A* genes can lead to dysfunction of *FOXP3* expression and thus to a loss of peripheral tolerance, which explains the increased risk of autoimmune pathology observed in KS patients.[2,8]

The study by Margot et al.[2] (2019) evaluated the presence of autoimmune diseases in a cohort of 177 KS patients in France. The mean age of the patients was 11.7 ± 10 years; 13.6% had an autoimmune disease. ITP was the most frequent (7.3%), followed by vitiligo (5,1%). One patient had DM1. The prevalence of autoimmune diseases increased with age, reaching 25.6% in the adult population (compared to 7.6% to 9.4% in the general population). The risk was higher in patients with immunodeficiency.

DM1 is the most common form of diabetes in children and adolescents and one of the most common chronic diseases in childhood, with a prevalence of 0.4% in middle-incidence countries and an increasing incidence in recent years. It is produced because of the autoimmune destruction of the beta cells of the pancreas, leading to insulin deficiency. A genetic predisposition is described within the etiopathogenesis of DM1,

Table 1. Diagnostic criteria for Kabuki Syndrome[6]

Definitive diagnosis: patient with a history of hypotonia, developmental delay, and/or intellectual disability and 1 or both major criteria:
Major criteria:
• A pathogenic or probably pathogenic mutation in the *KMT2D* or *KDM6A* genes.
• Typical dysmorphic features: long palpebral fissures with eversion of the external third of the lower lid and 2 or more of the following:
  • arched and sparse eyebrows in the outer third of the eyebrows
  • wide nasal bridge with depressed nasal tip
  • dysplastic ears
  • persistence of the fetal pads of the thumb of the fingers.
Other clinical manifestations that support the diagnosis: short stature, microcephaly, cleft palate, cleft palate, lip pits, dental alterations, hearing loss, congenital heart disease, feeding difficulties, genitourinary anomalies, brachydactyly, neonatal hypoglycemia, and immunological disorders.

Probable diagnosis: patients with a history of hypotonia, developmental delay, and/or intellectual disability and long palpebral fissures with eversion of the external third of the lower eyelid and at least 3 of these clinical manifestations.
Possible diagnosis: patients with a history of developmental delay and/or intellectual disability and at least 2 of these clinical manifestations + at least one of the following typical dysmorphic features: arched and sparse eyebrows in the outer third, broad nasal bridge with depressed nasal tip, dysplastic ears, and persistence of fetal finger pads.

Table prepared by the authors.

associated with environmental factors (including infections, dietary factors, microbiota alterations, and obesity).[4,10] DM1 in individuals with increased genetic risk can progress, at different rates, toward immune activation and the development of autoimmunity against the islets.[4,10] Its association with other autoimmune diseases is frequent; the most prevalent are Hashimoto's thyroiditis and celiac disease.[5]

Other publications report the association between DM1 and KS.[3,11] We highlight three pediatric patients with KS and DM1 in our case series, two of whom also had another associated autoimmune disease: thyroiditis and juvenile idiopathic arthritis.

KS requires a multidisciplinary team for follow-up. The diabetologist should be attentive to clinical manifestations that suggest the possibility of a genetic syndrome. ■

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