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# Síndrome de Kabuki e inmunodeficiencia

## Seguimiento y estudios de investigación en inmunodeficiencias primarias


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Retraso crecimiento

Facies característica


Alteración neurológica

Inmuno-deficiencia

Anomalias cardiacas

Retraso crecimiento

Facies característica


Alteración neurológica

Anomalias cardiacas

**Inmuno-deficiencia**

# ¿Qué es una inmunodeficiencia primaria?

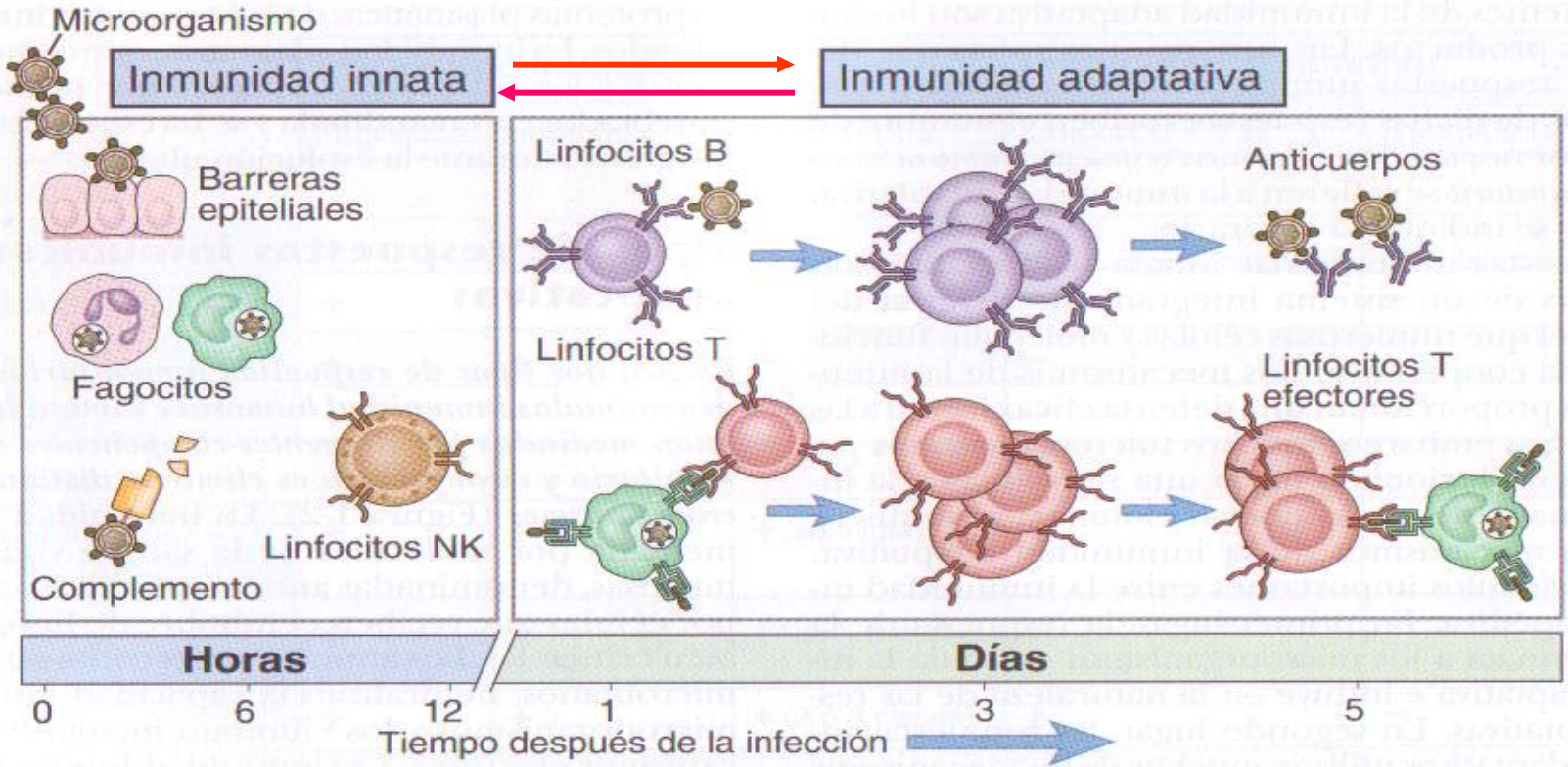
Grupo de enfermedades de causa genètica

↓

- Defecto **qualitativo o quantitativo** del sistema immunitario

- 1/2000 RN

- Clínica: **INFECCIONES**
  **Autoinmunidad** (artritis, anemia..)
  Alergia
  Proliferación celular benigna




*Inmunologia celular y molecular. K.Abbas Abul, H.Lichtman Andrew. 5ª Ed 2007*

¿Qué tipo de infecciones son las mas frecuentes en el síndrome de Kabuki?

↓

Infecciones respiratorias de vía superior (otitis) e inferior (neumonías)

↓

**Defecto humoral**

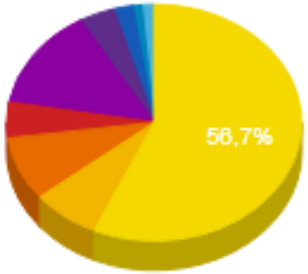
# Defecto humoral

Es el problema inmunitario **mas frecuente**

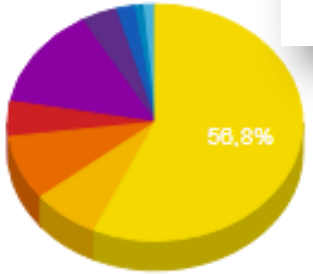
Un 60% de todas las inmunodeficiencias primarias son de tipo humoral

European Society for Immunodeficiencies

**2017**




**2016**

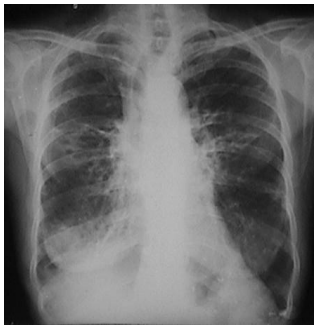



| Diagnosis | 2017 | | 2016 | |
|---|---|---|---|---|
| Predominantly Antibody Disorders | 56.66% | (n=10,966) | 56.78% | (n=10,629) |
| Predominantly T-Cell Deficiencies | 7.47% | (n=1,445) | 7.38% | (n=1,381) |
| Phagocytic Disorders | 8.73% | (n=1,689) | 8.89% | (n=1,664) |
| Complement Deficiencies | 4.89% | (n=946) | 4.82% | (n=903) |
| Other well defined PIDs | 13.91% | (n=2,693) | 13.85% | (n=2,592) |
| Autoimmune & immunedysregulation syndromes | 3.89% | (n=753) | 3.87% | (n=724) |
| Autoinflammatory syndromes | 2.06% | (n=398) | 2.01% | (n=377) |
| Defects in innate immunity | 1% | (n=193) | 0.98% | (n=183) |
| Unclassified PIDs | 1.41% | (n=272) | 1.43% | (n=267) |

# Defecto humoral

## Se caracteriza por

**Hipogammaglobulinemia** = descenso de inmunoglobulinas (Ig G, Ig M, Ig A) y a veces solo de Ig A  junto con disminución de linfocitos B de memoria y mala respuesta a vacunas



# Defecto humoral

## Clínica característica

Infecciones principalmente **bacterianas** de repetición del área respiratoria, ORL y gastrointestinal y posible daño orgánico (bronquiectasias a nivel pulmonar, **hipoacusia a nivel auditivo por otitis crónica…)**

**Table 1** Summary of all immunological characteristics reported for patients with Kabuki syndrome

| Age (years) | Sex | IgA | IgG | Autoimmunity | Infection history | Genetic analysis | References | Years |
|---|---|---|---|---|---|---|---|---|
| 1 | M | NA | NA | Sclerosing cholangitis | OM, UTI | NA | [52] | 1998 |
| 1 | F | ↓↓ | nl | – | PN | NA | [44] | 2002 |
| 1 | F | ↓ | nl | – | OM, UTI | NA | [9] | 2005 |
| 1 | F | ↓↓↓ | ↓↓ | – | – | NA | [9] | 2005 |
| 1 | M | ↓ | nl | – | OM, PN | NA | [9] | 2005 |
| 1 | M | ↓ | nl | – | OM, PN | NA | [9] | 2005 |
| 1 | M | ↓↓↓ | nl | – | OM | KMT2D: P2550Rfs2604X | [10] | 2014 |
| 1 | M | nl | nl | – | OM | KMT2D: Q5379X | [10] | 2014 |
| 2 | M | ↓↓↓ | nl | – | OM | KMT2D: C5109F | [10] | 2014 |
| 2 | M | ↓ | ↓ | – | PN | NA | [9] | 2005 |
| 3 | M | NA | NA | – | OM | KDM6A: c.2515_2518del | [7] | 2012 |
| 3 | F | ↓↓↓ | ↓ | VT, ITP, neutropenia | Chronic diarrhea | NA | [37] | 2004 |
| 4 | F | ↓ | nl | – | – | NA | [9] | 2005 |
| 4 | M | nl | nl | ITP, AIHA, leukopenia | – | NA | [11] | 2005 |
| 4 | F | nl | nl | Anemia (AIHA?) | UTI | NA | [36] | 2009 |
| 4 | M | nl | nl | ITP | OM | NA | [42] | 2001 |
| 5 | F | nl | ↓ | – | OM | NA | [9] | 2005 |
| 5 | M | nl | nl | – | OM | NA | [9] | 2005 |
| 5 | M | nl | nl | – | PN | NA | [9] | 2005 |
| 5 | M | nl | nl | ITP | OM | NA | | |
| 5 | F | NA | NA | Hyperthyroidism | OM | KMT2D: R1252X | | |
| 5 | F | ↓↓ | NA | HT, VT | – | NA | | |
| 6 | M | nl | ↓G2 | – | OM, UTI | NA | | |
| 6 | M | nl | nl | ITP | OM | NA | | |
| 6 | M | nl | nl | Arthritis? | PN, OM | NA | | |
| 6 | F | nl | ↓ | – | OM | KMT2D: R5500 W | | |

Immunol Res
DOI 10.1007/s12026-015-8707-4

INTERPRETIVE SYNTHESIS REVIEW ARTICLE

## Epigenetic control of the immune system: a lesson from Kabuki syndrome

Stefano Stagi[1] · Anna Virginia Gulino[2] · Elisabetta Lapi[1] · Donato Rigante[3]

# PRUEBAS DE LABORATORIO

## NIÑA 10 meses: Sana

| | | | | |
|---|---|---|---|---|
| **Immunoglobulines** | | | | |
| Pla-Immunoglobulina G | | 354 | mg/dL | 196.0 - 1045.0 |
| Pla-Immunoglobulina A | | 83 | mg/dL | 8.1 - 90.0 |
| Pla-Immunoglobulina M | * | 146 | mg/dL | 40.0 - 140.0 |

## Niño 7 años: SK

| | | | | |
|---|---|---|---|---|
| **Immunoglobulines** | | | | |
| Sm-Immunoglobulina G | * | 439 | mg/dL | 700.0 - 1600.0 |
| Sm-Immunoglobulina A | | 73 | mg/dL | 45.0 - 230.0 |
| Sm-Immunoglobulina M | * | 33 | mg/dL | 40.0 - 230.0 |

# PRUEBAS DE LABORATORIO

| | Ig G (mg/dL) | Ig A (mg/dL) | Ig M (mg/dL) |
|---|---|---|---|
| | | | |
| NNAT | 610 - 1.540 | 1 - 4 | 6 - 30 |
| 3 MESES | 170 - 560 | 5 - 50 | 30 - 100 |
| 6 MESES | 200 - 670 | 8 - 70 | 30 - 100 |
| 1 AÑO | 330 - 1.160 | 10 - 100 | 40 - 170 |
| 2-6 AÑOS | 400 - 1.100 | 10 - 160 | 50 - 180 |
| 7-12 AÑOS | 600 - 1.230 | 30 - 200 | 50 - 200 |
| ADULTOS | 700 - 1600 | 70 - 400 | 40 - 230 |

# ¿Por qué en el síndrome de kabuki se produce esta inmunodeficiencia?

SK se produce por mutaciones en KMT2D (70%) y en KDM6A (5%)

**H3K4-specific histone protein**

**Metilación**

**HOMEOSTASIS EN EL SISTEMA INMUNE**

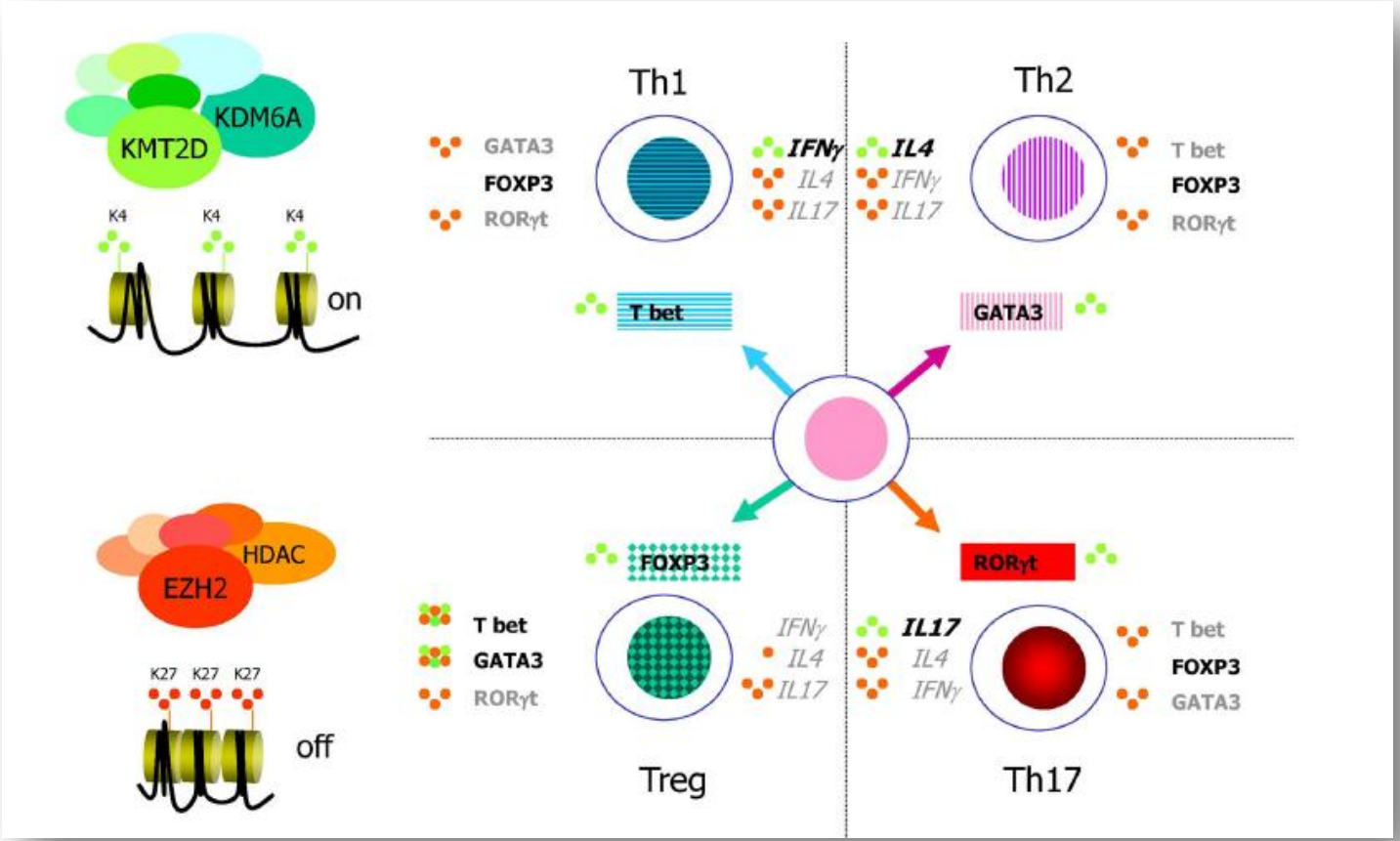
**Mantenimiento de células somáticas e inicio del proceso de "memoria" celular**

**Imprescindible en la diferenciación celular**

**SU DEFECTO = ALTERACIÓN EN LA MADURACIÓN DE LA RESPUESTA HUMORAL**

**ALTERACIÓN EN LAS CÉLULAS Tregs (= AUTOINMUNIDAD)**

**ALTERACIÓN EN LA DIFERENCIACIÓN CELULAR B (Y EN MENOR MEDIDA T)**




*Epigenetic control of the immune system: a lesson from Kabuki. 2015*

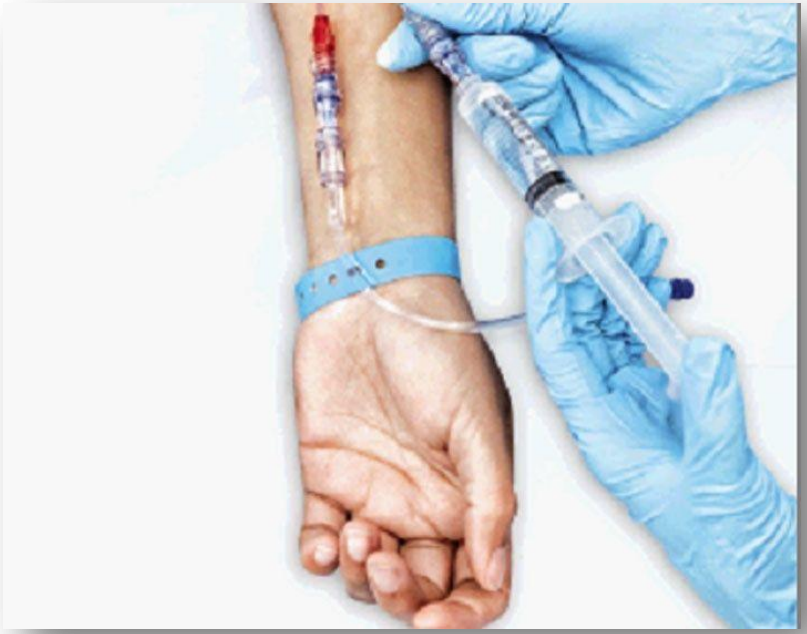
# ¿La evaluación inmunitaria es sencilla? ¿En que consiste?

En una analitica de sangre solicitando inmunoglobulinas, subclases de Ig G (> 7 años), linfocitos B (y T) y respuesta vacunal (> 2 años de edad) (con vacunación previa)

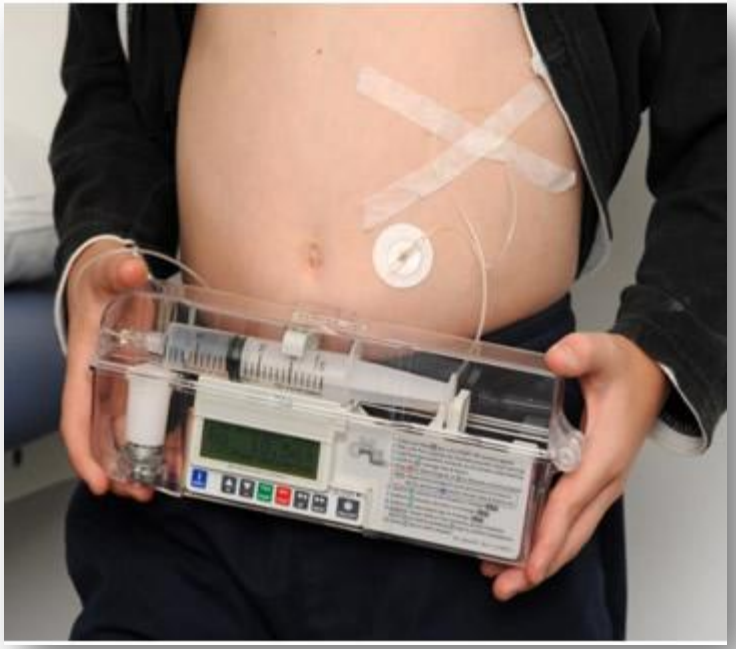
# Si se confirma defecto humoral y hay muchas infecciones…. ¿hay algún tipo de tratamiento?

Si, tratamiento con inmunoglobulinas intravenosas en hospital (cada 28 días) o subcutáneas en domicilio (cada 7-15 días o incluso CADA MES )

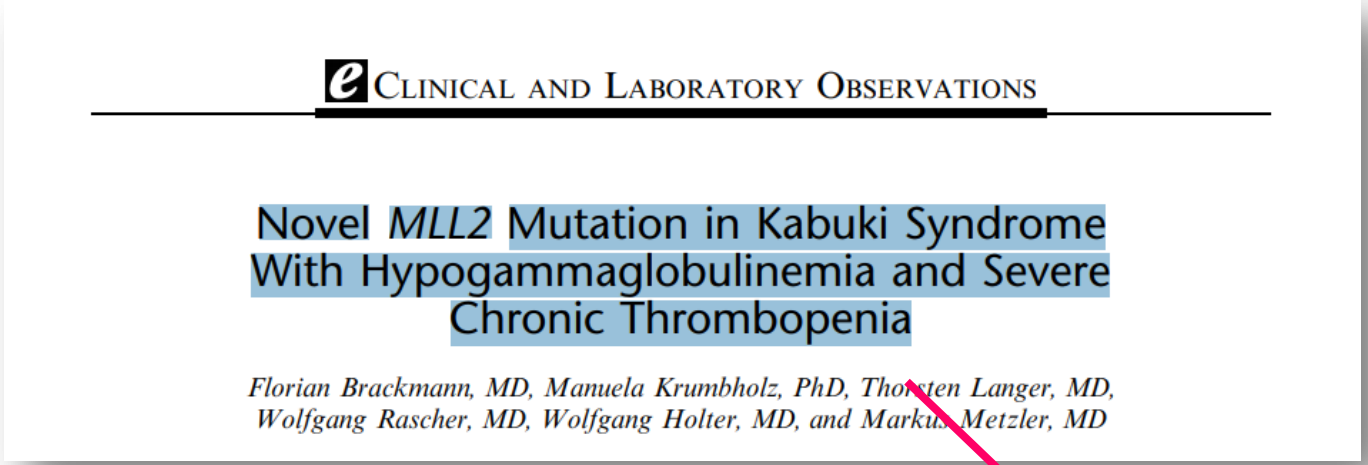
# IV



# SC



# REVISIÓN DE LA LITERATURA



e CLINICAL AND LABORATORY OBSERVATIONS

## Novel *MLL2* Mutation in Kabuki Syndrome With Hypogammaglobulinemia and Severe Chronic Thrombopenia

*Florian Brackmann, MD, Manuela Krumbholz, PhD, Thorsten Langer, MD, Wolfgang Rascher, MD, Wolfgang Holter, MD, and Markus Metzler, MD*

**POSIBILIDAD DE FENÓMENOS AUTOINMUNES**

# REVISIÓN DE LA LITERATURA

American Journal of Medical Genetics 132A:260–262 (2005)

## Autoimmune Disorders in Kabuki Syndrome

**Jeffrey E. Ming,* Karen L. Russell, Donna M. McDonald-McGinn, and Elaine H. Zackai**

*Division of Human Genetics and Molecular Biology, Department of Pediatrics, The Children's Hospital of Philadelphia and The University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania*

**Kabuki syndrome is associated with abnormalities in multiple organ systems. While many of the anomalies are congenital malformations, other clinical manifestations may not appear until later in childhood. Among these associated conditions, autoimmune abnormalities have been described in several patients. These include idiopathic thrombocytopenic purpura (ITP), hemolytic anemia, thyroiditis, and vitiligo. In this report, we describe five affected patients with autoimmune manifestations. Four patients had ITP, and two of these patients had concurrent hemolytic anemia. The fifth patient had vitiligo. Two of the patients with ITP had a chronic and relapsing course. Of note, some of these patients also had hypogammaglobulinemia. The autoimmune disorders may be manifestations of abnormal immune regulation. We conclude that Kabuki syndrome is associated with an increased incidence of autoimmune disorders. In addition, the presence of an underlying immune defect may predispose these children to a chronic course of these autoimmune conditions.** 

Philadelphia with autoimmune disease and propose that these conditions are a manifestation of Kabuki syndrome.

### CLINICAL REPORTS

#### Patient 1

This male patient presented with submucous cleft palate, hypodontia, lower lip pits, and hypospadias. He was noted to have short stature and developmental delay. On exam, he had long palpebral fissures, blue sclerae, prominent eyelashes, thinning of the central part of the eyebrow, mildly protuberant ears, and prominent fingertip pads (Fig. 1A). His karyotype was 46,XY, normal male, and subtelomeric analysis was normal. At the age of 13 years, he presented with a platelet count of 41,000/mm$^3$, and anti-platelet antibodies were detected. Although he had a normal hemoglobin level, he was noted to have an increased reticulocyte count. In addition, the peripheral blood smear was consistent with hemolytic anemia. He was diagnosed with ITP and an autoimmune hemolytic process. Although the ITP initially resolved, he had a relapse of ITP at age 20.

**POSIBILIDAD DE FENÓMENOS AUTOINMUNES**

# REVISIÓN DE LA LITERATURA

**An 18-year-old woman with Kabuki syndrome, immunoglobulin deficiency and granulomatous lymphocytic interstitial lung disease.**

De Dios JA[1], Javaid AA, Ballesteros E, Metersky ML.

**Author information**

**Abstract**

Granulomatous lymphocytic interstitial lung disease, or GLILD, is an uncommon condition associated with common variable immunodeficiency (CVID). We present an interesting case of an 18-year-old woman with Kabuki syndrome and CVID who was seen in our clinic for an abnormal chest CT scan. She was subsequently diagnosed with GLILD. There are no established guidelines for the treatment of GLILD in CVID. Immune globulin replacement therapy is the main treatment for CVID and higher doses of intravenous immunoglobulin (IVIG) may prevent the progression of chronic lung disease. Patients with CVID and GLILD are at increased risk for malignancy and their prognosis is worse compared to patients with CVID without GLILD.

**PROLIFERACIÓN CELULAR "BENIGNA"**

# REVISIÓN DE LA LITERATURA

**Kabuki (Niikawa-Kuroki) syndrome associated with immunodeficiency.**

Chrzanowska KH[1], Krajewska-Walasek M, Kuś J, Michałkiewicz J, Maziarka D, Wolski JK, Brecevic L, Madaliński K.

⊕ **Author information**

**Abstract**

We report a case of a 19-year-old male with the cardinal features of the Kabuki syndrome (KS) and, in addition, with severe immunodeficiency. Finding immune deficiency in a KS patient, prompted us to determine whether this association was related to a deletion within the DiGeorge chromosomal region. Fluorescence in situ hybridization (FISH) with the Oncor probe N25(D22S75) revealed no deletion of 22q11.2 in the patient.

**POSIBILIDAD DE INMUNODEFICIENCIA MAS GRAVE DE TIPO CELULAR (se afecta el linfocito T y pueden aparecer infecciones graves virales y por otros gérmenes)**

# ¿Evaluación y seguimiento desde el punto de vista inmunitario?

inical Management Guidelin

# Management of Kabuki Syndrome

**2011**

A Clinical Guideline

Kabuki Syndrome Guideline Development Group

e Clinical Management Guidelines

## Recommendations for the management of Kabuki Syndrome

*~ Immunology & Skin ~*

**All Ages**

| | | |
|---|---|---|
| **Immunity:** check levels of T cells, T cell subsets and immunoglobulins at diagnosis. | ABNL | If abnormal refer to paediatric immunologist for advice regarding any necessary immunisations. |
| | | Normal immunisation schedule may be followed if levels are normal. |
| | ABNL | Refer to an immunologist if there are recurrent infections. |
| **Respiratory tract infections:** | | Lower respiratory tract infections may have other causes apart from impaired immunity. These include aspiration pneumonia and anatomical variation of the bronchial tree. |
| **Autoimmune disease:** there is an increased risk of autoimmune disease, particularly: | | Check full blood count (FBC) and thyroid function every two to three years. |
| Idiopathic thrombocytopenic purpura | | Enquire about presence of purpura or symptoms of anaemia. |
| Autoimmune haemolytic anaemia | | |
| Vitiligo (benign condition, most likely with an autoimmune basis). | | The presence of vitiligo may also indicate autoimmune disease. |
| | ABNL | Refer to immunologist if autoimmune disease develops. |

# ASINTOMÁTICO

-Realizar analítica con niveles de inmunoglobulinas (a partir de los 4 años) y ver si hay alguna alteración (déficit de Ig A…) que requiera controles anuales

# SÍNTOMÁTICO CON OTITIS…

-Evaluación por ORL

-Realizar analítica con niveles de inmunoglobulinas y respuesta vacunal y si hay una hipogammaglobulinemia franca con respuesta vacunal anómala y muchas infecciones →

**gammaglobulina** (mínimo 2 a) para minimizar hipoacusia…

**Aunque se necesitan mas estudios para ver realmente esta eficacia**

# Estudios de investigación en SK

Hospital General Universitario Gregorio Marañón

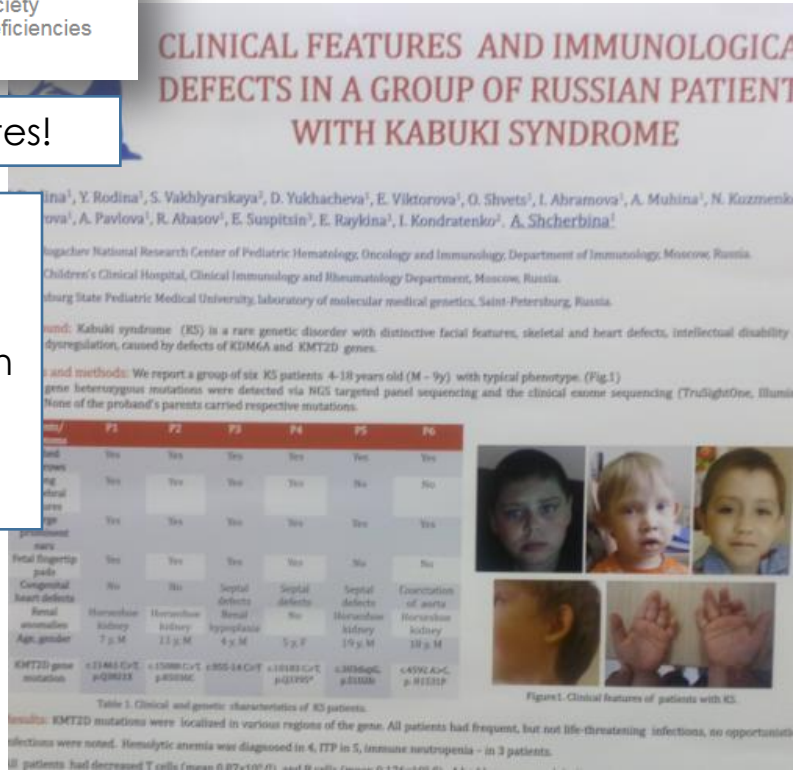
European Society for Immunodeficiencies

*Octubre 2017*

**Disfunción inmune en SK. Efectos sobre la homeostasis inmune, incidencia de enfermedades y evolución clínica en la población pediátrica**

6 pacientes!

Pendiente desarrollar un estudio multicentrico en Rusia con los pacientes con SK


CLINICAL FEATURES AND IMMUNOLOGICA
DEFECTS IN A GROUP OF RUSSIAN PATIENT
WITH KABUKI SYNDROME

# Estudios de investigación en in as

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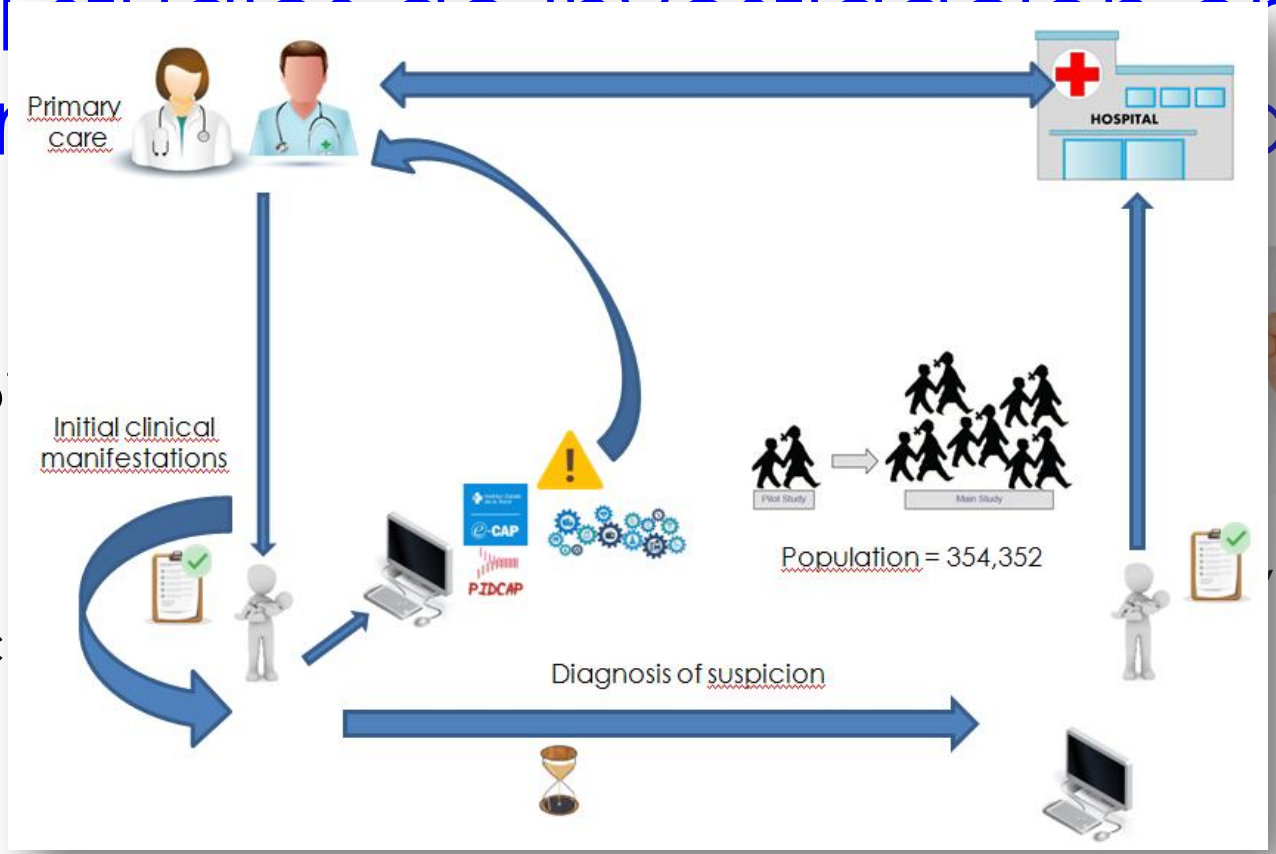


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# MUCHAS GRACIAS
# POR SU ATENCIÓN

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