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# A Complex Case of Koolen-De Vries Syndrome Associated with Hypopituitarism and Type 1 Diabetes Mellitus

# Um Caso Complexo de Síndrome de Koolen-De Vries Associado a Hipopituitarismo e Diabetes Mellitus Tipo 1

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**ABSTRACT**

Complex diseases arise from the interplay of genetic and environmental factors. We present a case where complex diseases seem to coexist. A 12-month-old girl was referred for short stature and hypotonia. Initial evaluation revealed central hypothyroidism, growth hormone deficiency and a small pituitary gland with ectopic neurohypophysis. Replacement therapy improved growth, but developmental delay and strabismus ensued. At age 10, she experienced a first seizure treated with levetiracetam. At age 12, she presented diabetic ketoacidosis and functional insulin therapy was started; positive autoantibodies confirmed autoimmune etiology. Initial genetic testing performed by microarray analysis retrieved normal results, but exome sequencing revealed a heterozygous pathogenic variant in *KANSL1* gene, allowing for the diagnosis of Koolen-de Vries syndrome. In this patient, Koolen-de Vries syndrome presented initially as hypopituitarism and only later epilepsy. Afterwards, type 1 diabetes *mellitus* ensued, highlighting the complexity of intertwined conditions.

**Keywords:** Abnormalities, Multiple; Chromosomes, Human, Pair 17; Diabetes Mellitus; Hypopituitarism; Intellectual Disability/genetics

**RESUMO**

As doenças complexas resultam da interação entre fatores genéticos e ambientais. Apresentamos um caso de aparente coexistência de várias doenças complexas. Uma criança do sexo feminino foi referenciada aos 12 meses por má progressão estaturoponderal e hipotonia. A avaliação inicial revelou hipotiroidismo central, deficiência de hormona de crescimento e hipófise pequena com neuro-hipófise ectópica. A terapêutica de substituição melhorou o crescimento, mas foram surgindo atraso de desenvolvimento e estrabismo. Aos 10 anos, teve a primeira crise epilética sendo medicada com levetiracetam. Aos 12, apresentou-se com cetoacidose diabética iniciando insulinoterapia funcional; autoanticorpos positivos confirmaram a etiologia autoimune. O estudo inicial por *microarray* foi normal, mas a sequenciação do exoma revelou uma variante patogénica no gene *KANSL1*, levando ao diagnóstico de síndrome de Koolen-de Vries. Nesta doente, a apresentação foi inicialmente hipopituitarismo e mais tarde epilepsia. Posteriormente, surgiu diabetes *mellitus* tipo 1, ilustrando a complexidade deste caso.

**Palavras-chave:** Anormalidades Múltiplas; Cromossomos Humanos Par 17; Deficiência Intelectual/genética; Diabetes Mellitus; Hipopituitarismo

## INTRODUCTION

Koolen-de Vries syndrome (KdVS; OMIM #610443) is a genetic syndrome characterized by congenital malformations, hypotonia, developmental delay and intellectual disability, and epilepsy.[1,2] Congenital malformations comprise structural brain anomalies, congenital heart defects, and renal and urologic anomalies. Patients can rarely present with endocrine alterations.[3] The syndrome is usually diagnosed in patients with typical clinical findings associated either with a heterozygous deletion at chromosome 17q21.31 encompassing the *KANSL1* gene in 60% of cases, a heterozygous intragenic pathogenic variant in 40% of cases, or an haploinsufficiency (whenever one of the copies of a gene is inactivated and the functional copy is not sufficient, not guaranteeing adequate production of the protein) of *KANSL1* due to chromosome rearrangements (less than 1%).[3,4]

Complex diseases are defined by the interference of different genetic and environmental factors, and the contribution of each factor is often hard to unravel.

## CASE REPORT

A 12-month-old girl was referred to the outpatient clinic for growth failure and hypotonia. Family history was unremarkable. She was the first daughter of a healthy non-consanguineous couple.

Following an uneventful pregnancy, birth occurred at 40 weeks of gestation by vacuum delivery, with birth weight 3075 g (-0.35 SD), length 47 cm (-1.15 SD) and cranial perimeter 34.5 cm (+0.52 SD).

At the first visit, her weight was 8.055 kg (-1.6 SD) and her length 72 cm (-2.0 SD). Her growth chart showed a deflection of the length curve from five months on; at nine months, her growth was already at -2 SDS. Some dysmorphic features were noticed, namely a triangular face, prominent ears, as well as mild axial hypotonia.

Since a previous laboratory workup had revealed central hypothyroidism and growth hormone deficiency (IGF1 < 25 ng/mL), replacement therapy with levothyroxine had been started. In our first evaluation, she displayed normal

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thyroid function. Cranial magnetic resonance imaging (MRI) showed a small pituitary gland with an ectopic neurohypophysis.

Replacement therapy with growth hormone was started at 16 months. The growth response was positive, with catch up growth from -2SDS to normal (Fig. 1); ACTH deficiency was suspected, with cortisol 3.2 ug/dL (reference range 3 - 21 ug/dL) and ACTH 11.3 pg/mL (reference range < 46 pg/mL), and as such, stress-dose hydrocortisone was prescribed.

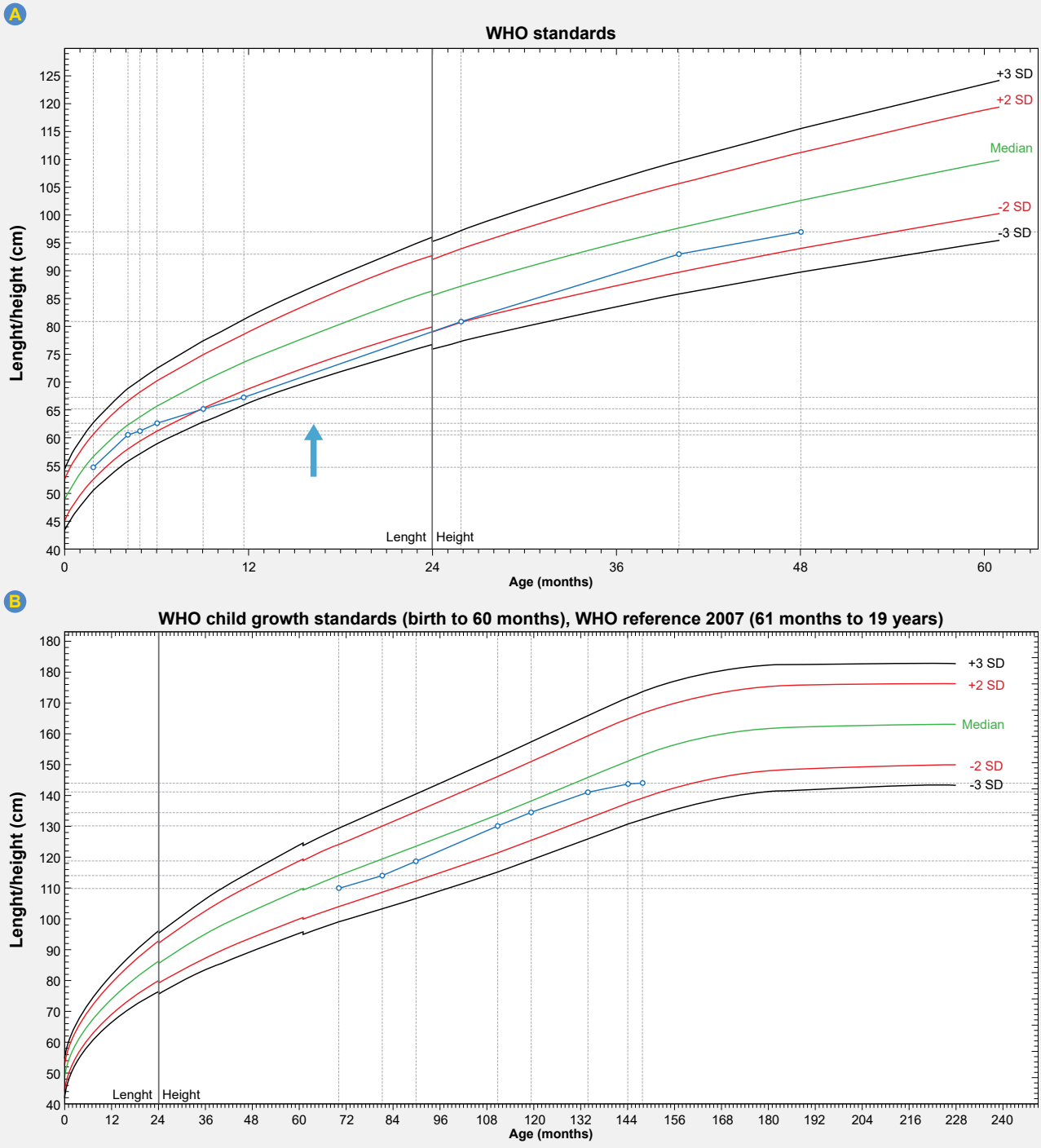


Figure 1 – Height charts showing a decline followed by catch up growth after the initiation of GH at 16 months (arrow). (A) Until 5 years (60 months). (B) From 5 years to present age.

During the third year of life, development delay and strabismus became apparent. At this time, she underwent molecular karyotyping, microarray, that did not reveal pathogenic copy number variants.

At the age of ten, she had a tonic-clonic seizure, starting anti-convulsive therapy, without further seizures. A cranial magnetic resonance imaging (MRI) was repeated, confirming a hypothalamic-pituitary malformation characterized by a thin pituitary stalk, ectopic neurohypophysis, ill-defined infundibular recess, hypertrophy of the interhypothalamic adhesion but revealing also mesencephalic-diencephalic dysplasia, corpus callosum dysgenesis, and inferior temporal dysgyria (abnormal gyral pattern in which the cortical surface is normally layered but the sulci course at unusual angles and depths) with slight alteration in hippocampal rotation (Fig. 2).

Comprehensive genetic testing through solo exome sequencing revealed a heterozygous *KANSL1* pathogenic variant which established the diagnosis of KdVS: *KANSL1* (NM_001193466.1) - c.(2666+1_2667-1)_(2724+1_2725-1) del.

Pediatric cardiology evaluation showed mitral valve prolapse with mild regurgitation, without hypertension; these findings are not usually associated with KdVS.

At the age of 12 years, she was observed at our emergency department due to vomiting, polydipsia, and polyuria. Laboratory evaluation showed: glycemia 423 mg/dL, high blood ketones, pH 7.18, bicarbonate 12.8, allowing for the diagnosis of diabetic ketoacidosis. Antibodies to glutamic acid decarboxylase, IA2 and insulin were positive, corroborating an autoimmune etiology.

Treatment with multiple daily insulin administration was started. Two months later, she changed to an automated insulin delivery pump. Now, eleven months after this diagnosis, excellent metabolic control has been achieved (time in range: 82%, HbA1c: 5.2%). The patient currently presents positive anti-thyroglobulin antibodies (294 IU/mL; Reference range < 115 IU/mL). The present height is 146.7 cm (-1.62 SD). She attends a regular school, although with an adapted curriculum.

## DISCUSSION

First described in 2006, KdVS can present as early as the neonatal period, with hypotonia and feeding difficulties. While mild-to-moderate development delay is paramount, with speech and language particularly affected, progressive dysmorphic craniofacial features such as a broad nasal root and a large columella may appear. Central nervous system imaging often reveals structural abnormalities such as ventriculomegaly, corpus callosum hypoplasia, and Arnold-Chiari malformation.[3]

The present case presents not only the MRI features usually described in KdVS but also a less commonly described malformation, affecting both the pituitary and the hypothalamic region.[3,5,6] Even though very thin pituitary stalk and absent posterior neurohypophysis signal have been described by El Chehadeh-Djebbar *et al* in one case of KdVS, such a complex malformation involving the hypothalamic region has not been reported to the best of our knowledge.[7] Interestingly, while both cases display the commonly found corpus callosum hypoplasia, none featured optic nerve abnormalities that would suggest septo-optic dysplasia.

Koolen-de Vries syndrome is typically caused by a 17q21.31 deletion encompassing the NSL regulatory complex subunit 1 gene *KAT8* (*KANSL1*) or a point variant in the *KANSL1* gene. Molecular genetic testing approaches may include a combination of microarray, a multigene panel, and more comprehensive genomic testing. Penetrance is reported to be 100%.[3] The identified variant has not been previously described to the best of our knowledge. Parental segregation studies are warranted, such as genetic counseling, in order to better characterize recurrence risks.

Endocrine alterations such as hypothyroidism, hypopituitarism, primary adrenal insufficiency, and precocious

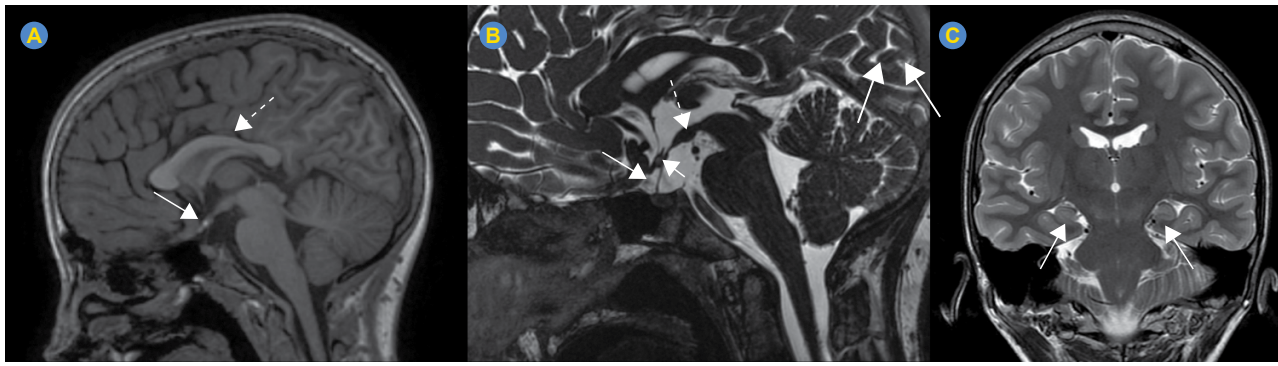


Figure 2 – Structural brain anomalies. (A) Sagittal T1 weighted image. (B) Sagittal volumetric T2 weighted image. (C) Coronal T2 weighted image. Hypothalamic-pituitary malformation characterized ectopic neurohypophysis (arrow in A), thin pituitary stalk (arrow in B), ill-defined infundibular recess (small arrow in B), hypertrophy of the interhypothalamic adhesion (dashed arrow in B); corpus callosum dysgenesis (dashed arrow in A); slight alteration in hippocampal rotation (arrows in C).

puberty have previously been described in KdVS, albeit infrequently (< 10%),[3,6] but, to our knowledge, only one patient with both type 1 diabetes and KdVS has been described.[8] Even though no causality can be established, these are not the only reports of immune disruption associated with the syndrome. *KANSL1* may be a gene that interferes in immune-response gene expression, being in a structurally complex genomic region.[9] Vitiligo, Addison and celiac diseases have also been described, and it has been hypothesized that autoimmunity may play a role in KdVS.[6,10,11]

While debate ensues on whether these diagnoses are pathogenically associated, our patient and her family face multiple difficulties, resulting from dealing with the consequences of complex diseases, namely hypopituitarism, development delay, and type 1 diabetes *mellitus*. Further investigation is warranted for a deeper understanding of the mechanisms and interactions of these entities, allowing for more precise and targeted treatment.

## PREVIOUS AWARDS AND PRESENTATIONS

Presented as a poster at the 62nd Annual ESPE Meeting (ESPE 2024).

## AUTHOR CONTRIBUTIONS

MFC: Writing of the manuscript.

FBC, DA, LL: Critical review of the manuscript.

CC: Data analysis, critical review of the manuscript.

All authors approved the final version to be published.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## PARENTAL CONSENT

Obtained.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest related to this work.

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