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BRIEF REPORT

# Peripheral precocious puberty: 46,XY complete gonadal dysgenesis☆

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**Abstract** Despite standard clinical definitions and availability of diagnostic tests for precocious puberty, an intensive and structured investigation is needed in order to diagnose the aetiology in particular cases.

A 4-year-old, phenotypically female child was referred to paediatric endocrinology consultation for premature pubarche and thelarche. There was an acceleration of growth velocity with high levels of oestradiol and testosterone, and prepubertal FSH and LH measurements. Investigation showed bilateral gonadoblastoma as the cause of the peripheral precocious puberty.

Genetic studies revealed 46,XY karyotype with mutation c.89G>T (p.Arg30Ile) in exon 1 of the SRY gene, confirming the diagnosis of complete gonadal dysgenesis. Disorders of sexual differentiation must be considered in the approach and investigation of peripheral precocious puberty, especially in the presence of ovarian tumours, such as gonadoblastoma and dysgerminoma.


**PALABRAS CLAVE**
Disgenesia gonadal;
Gonadoblastoma;
Pubertad precoz

**Pubertad precoz periférica: disgenesia gonadal completa 46 XY**

**Resumen** La pubertad precoz, a pesar de las definiciones clínicas estandarizadas y pruebas de diagnóstico disponibles, requiere, en ciertas situaciones una investigación exhaustiva y estructurada con el fin de conocer la causa.

Niña de 4 años de edad, fenotípicamente de sexo femenino, enviada a la consulta de endocrinología pediátrica por pubarquia y telarquia. Se observó aceleración en la tasa de

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crecimiento con niveles altos de estradiol y testosterona, con determinaciones prepúberes de la hormona luteinizante y foliculoestimulante. El resto del estudio de pubertad precoz periférica mostró la presencia de gonadoblastoma bilateral. El estudio genético reveló cariotipo 46 XY con mutación c.89G> T (p.Arg30Ile) en el exón 1 del gen SRY, confirmando el diagnóstico de disgenesia gonadal completa.

Los trastornos de la diferenciación sexual deben ser considerados en el abordaje y la investigación de las causas de la pubertad precoz periférica, especialmente en presencia de tumores de ovario, como gonadoblastoma y disgerminomas.


## Introduction

Precocious puberty (PP) is defined as the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys.[1,2]

The aetiology of PP is diverse, ranging from variations of normal development, such as isolated premature thelarche, to diseases with significant comorbidity and mortality, such as germ cell tumours.

Addressing PP involves classifying it into two subtypes: central precocious puberty (CPP), which is gonadotropin-dependent (caused by early maturation of the hypothalamic–pituitary–gonadal [HPG] axis) and peripheral precocious puberty (PPP), which is gonadotropin-independent (due to excess secretion of sex hormones, androgens or oestrogens, from the adrenal glands, the gonads or exogenous sources).[2]

PPP may be of genetic origin (testotoxicosis; congenital adrenal hyperplasia; *DAX1* gene mutation; McCune–Albright syndrome) or acquired (ovarian cyst; ovarian, testicular or adrenal tumours that produce the β subunit of human chorionic gonadotropin [β-hCG]); exogenous sex steroids).[3]

Acquired PPP occurs secondary to an increase in exogenous or endogenous sex steroids.

Diagnostic assessment includes an anamnesis and a detailed physical examination and additional tests, such as determination of basal and LHRH-stimulated gonadotropin levels (essential for differential diagnosis between CPP and PPP), hormone tests (testosterone, 17-β-oestradiol, dehydroepiandrosterone sulphate [DHEA-S], androstenedione and 17-hydroxyprogesterone [17-OH-progesterone], β-HCG, free thyroxine [free T4] and thyroid-stimulating hormone [TSH]) and imaging tests (hand-wrist radiograph to determine bone age, pelvic or testicular and abdominal ultrasound and cranial MRI). Finally, in the presence of strong clinical suspicion, genetic testing should be performed.[3]

## Case history

Girl referred to paediatric endocrinology consultation at the age of 4 years 2 months with suspected precocious puberty.

She had been born to term with adequate somatometry for her gestational age and no important family, perinatal or pathological history.

She presented with appropriate psychomotor development for her age and her height and weight development. Her weight was above the 95th percentile with upward centile crossing, having ranged from the 25th to the 50th percentile up to age 2 and then crossed to values above the 95th percentile by the age of 4 (Fig. 1).

Development of secondary sexual characteristics was observed at age 4, with the appearance of pubic hair and breast budding. In her first hospital assessment her weight was 22 kg (>95th percentile), height 115.5 cm (standard deviation score [SDS] 3.10), growth velocity 14.81 cm/year (SDS 7.13), target height 159 cm (SDS −0.50) and external female genitalia with Tanner stage A1-B2-P2.

Laboratory tests revealed high levels of oestradiol, total testosterone and β-HCG (Table 1).

The levels of 17-OH-progesterone, DHEA-S, delta-4-androstenedione, free T4, TSH, adrenocorticotropic hormone, cortisol (morning level), prolactin, lactate dehydrogenase (LDH) and alpha-foetoprotein (α-FP) were normal for her age (Table 1). Serum FSH was 0.3 mU/mL and LH < 0.1 mU/L, and the LH/RH test showed a prepubertal response (peak LH 1.1 mU/mL; peak FSH 2.3 mU/mL, LH/FSH ratio <1).

Bone age (BA) was 19 months in advance of chronological age (CA) (BA: 5 years 9 months, CA: 4 years 2 months). The pelvic ultrasound revealed a focal, well-circumscribed hyperechoic mass 25 mm in diameter in the left adnexal region. The pelvic computed tomography revealed bilateral solid adnexal lesions, with calcified matrix, measuring 30 mm on the right and 25 mm on the left.

Histological examination of the biopsy specimen showed patches of tissue occupied by bilateral gonadoblastoma structures, confirmed by immunohistochemistry (CD117 and inhibin-alpha).

A laparoscopic bilateral oophorectomy was performed. Anatomohistopathological analysis confirmed the presence of bilateral gonadoblastoma (Figs. 2 and 3).

Genetic testing of peripheral blood revealed a 46,XY karyotype with mutation c.89G>T (p.Arg30Ile) in exon 1 of the *SRY* gene (sex-determining region of the Y chromosome), which confirmed the diagnosis of complete XY gonadal dysgenesis due to a mutation in the *SRY* gene.

## Discussion

Gonadoblastomas are rare benign tumours composed of germ cells mixed with circumscribed nests of sex cord cells, generally with a hyaline basement membrane and with diffuse or focal calcifications.[4] They were first described by Scully in 1953.[5]