Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 03/09/2020
Approved on: 03/27/2020

CASE REPORT

Familial central precocious puberty due to inactivation of the MKRN3 gene: case report

Carolina de Oliveira Cavalcanti Assumpcao[1], Luciana Ribeiro Montenegro[2], Paulo Ferrez Collett-Solberg[3], Daniel Luis Schueftan Gilban[4],Ana Paula Neves Bordallo[4], Clarice Borschiver de Medeiros[4], Ana Claudia Latrônico[2], Isabel Rey Madeira[5]

Keywords:
Puberty,
Precocious,
Genetics,
Mutation.

Abstract

Central precocious puberty results from premature activation of the hypothalamic-pituitary-gonadal axis. The factors involved in central early puberty are still poorly understood. Recently, mutations in the makorin ring finger protein 3 (MKRN3) gene have been identified in familial cases. We report the case of two sisters with central precocious puberty. The diagnosis, carried out by molecular analysis, showed an inactivating mutation of the MKRN3 gene.

[1] University of the State of Rio de Janeiro- Pedro Ernesto University Hospital, Resident Physician in Pediatric Endocrinology - Rio de Janeiro - RJ - Brazil.
[2] University of São Paulo (USP). Faculty of Medicine (FM), Developmental Endocrinology Unit, Laboratory of Hormones and Molecular Genetics/LIM42 - São Paulo - SP - Brazil.
[3] Pedro Ernesto University Hospital, State University of Rio de Janeiro, Adjunct Professor at the Endocrinology and Metabology Teaching Unit of the Internal Medicine Department of the UERJ Medical Sciences Faculty. Physician of the Pediatric Endocrinology Sector of the Endocrinol Teaching Care Unit - Rio de Janeiro - RJ - Brazil.
[4] Pedro Ernesto University Hospital - Rio de Janeiro State University, Physician in the Pediatric Endocrinology Sector at the Endocrinology Care Teaching Unit at HUPE-UERJ. Preceptor of the Medical Residency Program in Pediatric Endocrinology at the Pedro Ernesto University Hospital - Rio de Janeiro - RJ - Brazil.
[5] Pedro Ernesto University Hospital - State University of Rio de Janeiro, Associate Professor at the Department of Pediatrics, Faculty of Medical Sciences, UERJ, coordinator of the Pediatric Endocrinology Sector of the Endocrinology Care Teaching Unit at HUPE-UERJ. Supervisor of the Medic Residency Program - Rio de Janeiro - RJ - Brazil.

Correspondence to:
Carolina de Oliveira Cavalcanti Assumpção.
Pedro Ernesto University Hospital. Boulevard 28 de Setembro, nº 77, Vila Isabel, Rio de Janeiro, RJ, Brasil. CEP: 20551-030. E-mail: cocassumpcao@gmail.com

DOI: 10.25060/residpediatr-2022.v12n1-281

This work is licensed under a Creative Commons Attribution 4.0 International License.

INTRODUCTION

Central precocious puberty (CPP) is defined by the emergence of secondary sexual characteristics through maturation in the hypothalamic-pituitary-gonadal axis, before 8 years of age in girls and 9 years in boys, or by menarche before 9 years of age in girls[1]. Rapidly progressive puberty, although initiated at normal age, presents a rapid evolution, with a rapid change of pubertal stage in a period of less than 3 months and acceleration of bone maturation, resulting in the loss of final height. Familial PPC is defined by its occurrence in two or more family members[2].

In PPC, there is an increase in the pulsatile secretion of gonadotropin-stimulating hormone (GnRH) in the portal-pituitary circulation, which acts on the anterior pituitary gland, stimulating the secretion of gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), in the circulation. peripheral.

GnRH secretion is coordinated by a complex neuronal network, made up of secretory neurons with inhibitory or stimulatory actions, involving genetic, environmental, metabolic, nutritional factors and neurological alterations. There are also idiopathic forms, when congenital or acquired lesions in the central nervous system (CNS) and monogenic defects are excluded[2]. Many of these factors are still poorly understood. The incidence of PCP found in a population-based study in Denmark is 20 cases per 10,000 girls and 5 cases per 10,000 boys[3,4]. Idiopathic forms represent 90% in girls. On the other hand, in 50-70% of boys the origin is organic, such as CNS tumors, inflammatory diseases or CNS infections[1,4].

In 2013, it was described for the first time by Abreu et al.[5], the role of the *makorin gene ring finger protein 3 (MKRN3*) in the pathogenesis of PPC, representing 46% of familial cases and 5% of sporadic cases. Until then, only activating mutations of the *kisspeptin-kisspeptin receptor 1 system (KISS1 and KISS1R*) had been described as a genetic cause of PPC. MKRN3 is a single exon gene located on chromosome 15. It *is imprinted on the* mother and is expressed only by the paternal allele. It is believed that *MKRN3* encodes a transcription factor with an inhibitory effect on GnRH secretion and, when inactive, triggers a premature activation of the HHG axis, leading to a PPC. New genes are being discovered in this pathogenesis. In 2013, described by Abreu et al.[5], a mutation in the DKL1 gene, presenting, similarly to MKRN3, an inactivating mutation with expression in the paternal allele.

These recent findings mean that the previously described epidemiological data of PPC, of idiopathic origin, are being reassessed.

CASE REPORT

Patient No. 1

MCGB, female, white, referred to the referral pediatric endocrinology service at 8 years and 8 months, born in Rio de Janeiro, born by cesarean section, suitable for gestational age (AGA). History of thelarche and pubarche starting at 6 years of age and accelerating growth velocity.

In this first consultation at the service, she brought the following exams, performed at 7 years of age: LH 7.4UI/L (VR<0.2UI/L), FSH 10.1UI/L (VR: up to 3.3UI/L); pelvic ultrasound (USG) with description of "uterine volume 23.3cc, right ovary 5.9cc, left ovary 3.2cc and presence of follicles"; magnetic resonance imaging (MRI) of sella turcica without alterations. He also brought the radiograph of the left hand and wrist which, evaluated by the method of Greulich and Pyle (1959)[6] showed a bone age (OI) of 11 6/12 years with a chronological age (CI) of 8 2/12 years.

The patient was using a GnRH analogue at a dose of 7.5mg, started at 7 years and 9 months.

Family history: father, 35 years old, measuring 160 cm. Mother, 38 years old, measuring 158 cm, onset of puberty at 10 years old, menarche at 12 years old. Paternal aunt had menarche at age 7. Calculation of target height, using the formula (girl = [mother's height + father's height - 13] ÷ 2) proposed by Tanner (1986)[7]: 152.5cm.

On physical examination: atypical facies, normal thyroid on ectoscopy and palpation, absence of lymph node enlargement. Pubertal development according to Marshall and Tanner (1969)[8], 3 for breasts and 2 for pubic hair. Height: 136cm (z score: +0.92), proportional; weight: 37kg (Z score:+1.7); body mass index (BMI): 20kg/m^2 (Z score: +1.7).

Patient No. 2

MGB, female, white, referred to the referral pediatric endocrinology service at 6 years and eight months, born in Rio de Janeiro, cesarean delivery, AIG. Maternal report of thelarche at 5 years of age, absence of pubarche, with accelerated growth velocity. Patient 1's sister.

Bringing in this first consultation complementary exams that were performed at 6 years of age **:** LH 3.1UI/L and FSH 9.2UI/L. Pelvic USG with description of "uterine volume: 1.6cc, right ovary 2.4cc and left ovary 1.4cc. Radiographs of the left hand and wrist assessed by the method of Greulich and Pyle (1959)[6] showed an OI of 7 10/12 years with a CI of 6 4/12 years. MRI of sella turcica without changes.

On physical examination: atypical facies, normal thyroid on ectoscopy and palpation, absence of lymph node enlargement. Pubertal development according to Marshall and Tanner (1969)[8], 2 for breasts and 1 for pubic hair. Height: 124cm (Z score:+0.95) proportional, weight: 27.9kg (Z score:+1.6) BMI: 18kg/m^2 (Z score:+1.4).

She was also referred to the reference service using a GnRH analogue at a dose of 7.5mg, starting at 5 years and 9 months.

MKRN3 gene was performed in both sisters and the father, using the Sanger method[5], and an inactivating mutation was observed (mutation: c.1172_1173insA p.Tyr 391fs (rs879255239), confirming the familial form of PPC of paternal inheritance.

DISCUSSION

CPP is defined as the emergence of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys, however, recent epidemiological studies have shown that in the United States of America, the onset of puberty in girls has occurred earlier. The appearance of thelarche and pubarche was observed on average 1 year earlier in white girls and 2 years earlier in African- American girls . This anticipation may be associated with overweight and obesity, ethnic origin and endocrine disruptors[1,9].

Accurate diagnosis of PPC and adequate indication of treatment with GnRH analogues are challenging. A careful history, physical examination, exclusion of CNS lesion, assessment of bone maturation and growth velocity are of paramount importance. Serum levels with an increase in LH and FSH correspond to activation of the HHG axis, and the gold standard test for assessing the activation of the HHG axis is baseline serum LH and after stimulation with a GnRH analogue[4].

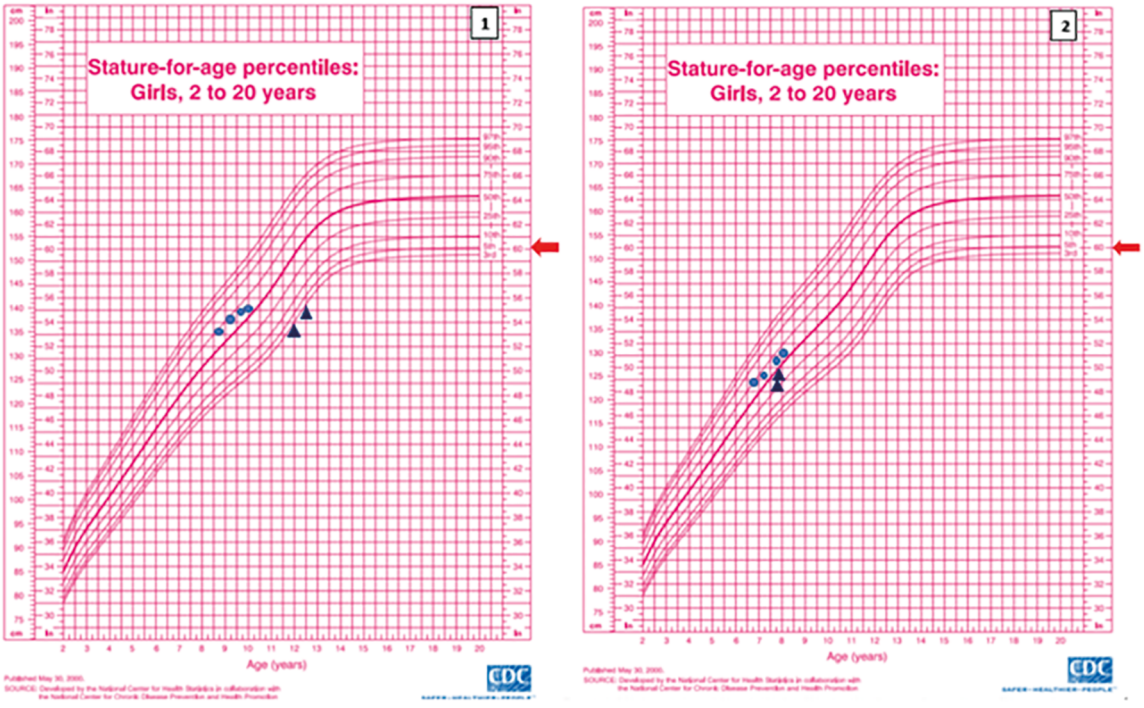
Treatment aims to interrupt sexual maturation until the child reaches the physiological age for development, being able to reverse or stabilize the evolution and delay skeletal maturation, aiming to preserve the final height within the child's genetic target. The psychosocial issues involved are also taken into account[10]. It is performed with a GnRh analogue, with an initial dose of 3.7mg every 28 days, being evaluated regularly, according to clinical, laboratory and radiological evolution.

It is believed that most of the girls evaluated at this borderline age (6-8 years) do not need treatment, since no benefit was observed in final height and in up to 50% of cases, spontaneous regression occurs[4]. However, it is necessary to exclude rapidly progressive PP and assess psychosocial factors that may justify treatment.

In the cases described above, there was an important family history of PP because, according to reports, the paternal aunt had menarche at age 7 and the father had short stature, possibly due to PP. In this context, an evaluation with *MKRN3 genetic sequencing was requested* for the patients and their father, since, as observed by Abreu et al. (2013)[5], this gene undergoes maternal *imprinting* , being expressed only by the paternal allele, as suggested by the family history of the cases in question. An inactivating mutation of the MKRN3 gene was documented in both patients and in the father.

The clinical features of PPC caused by inactivating mutations of *MKRN3* are indistinguishable from other idiopathic PPCs. To date, no notable clinical or hormonal features that differentiate patients with *PPC* caused by mutations in *MKRN3* [5 have been identified]. It has even been observed that patients with genetic causes of CPP present adequate clinical and laboratory responses to GnRH analogues , similar to patients with idiopathic CPP[2].

Case 1 had started treatment at 7 years and 9 months. We observed (Graph 1.1) that the beginning of the treatment already presented an advanced bone age in relation to the



Graph 1. Height x age. Left: patient #1; right graph: patient #2. Red seven: genetic target 152.5cm. Black triangle: bone age. Final height prediction: case 1, 152cm; case 2, 163cm.

chronological age, due to the probable delay in the diagnosis of PCP and the beginning of the treatment, with a prediction of the final height slightly below the genetic target.

Case 2 had started treatment at 5 years and 9 months. We observed (in Graph 1.2), a better evolution for having started the treatment early, without an acceleration of bone maturation and a significant loss of stature.

Despite the great advance with new discoveries, the diagnosis and treatment of central precocious puberty still represents a great challenge.

The genetic analysis of *MKRN3*, in the presence of an important family history, should be included in the investigation, since its incidence in cases of familial CPP is significant, as described by Abreu et al. (2013)[5]. And the earlier the diagnosis of CPP, the better the prognosis in cases where treatment is needed.

REFERENCES

1. Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. Lancet Diabetes Endocrinol. 2016 Mar;4(3):265-74.
2. Canton AP, Seraphim CE, Brito VN, Latronico AP. Pioneering studies on monogenic central precocious puberty. Arch Endocrinol Metab. 2019 Ago;63(4):438-44.
3. Abreu AP, Dauber A, Macedo DB, Noel SD, Brito VN, Gill JC, et al. Central precocious puberty caused by mutations in the imprinted gene MKRN3. N Engl J Med. 2013 Jun;368(26):2467-75.
4. Teilmann G, Pedersen CB, Jensen TK, Skakkebaek NE, Juul A. Prevalence and incidence of precocious pubertal development in Denmark: an epidemiologic study based on national registries. Pediatrics. 2005 Dez;116(6):1323-8.
5. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969 Jun;44(235):291-303.
6. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford: Stanford University Press; 1959.
7. Tanner JM. The use and abuse of growth standards. In: Falkner F, Tanner JM, eds. Human growth. 2nd ed. New York: Plenum; 1986. vol. 3. p. 95-112.
8. Kaplowitz P. Update on precocious puberty: girls are showing signs of puberty earlier, but most do not require treatment. Adv Pediatr. 2011;58(1):243-58.
9. Carel JC, Léger J. Clinical practice. Precocious puberty. N Engl J Med. 2008 Mai;358(22):2366-77.
10. Brito VN, Spinola-Castro AM, Kochi C, Silva PCA, Guerra-Júnior G. Central precocious puberty: revisiting the diagnosis and therapeutic management. Arch Endocrinol Metab. 2016 Abr;60(2):163-72.