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RESEARCH

The role of MKRN3 gene on central precocious puberty

Santral erken pubertede MKRN3 geninin rolü

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Abstract

Purpose: Central precocious puberty (CPP), which is characterized by premature activation of the hypothalamus-pituitary-gonadal axis, is more common in girls. Although genetic factors, such as mutations in MKRN3, have been identified, their role in CPP remains a subject of investigation. This study aimed to evaluate the role of MKRN3 in CPP development.
Materials and Methods: This retrospective study included 70 patients with CPP. Demographic, anthropometric, and laboratory data were collected. Genetic analysis of *MKRN3* pathogenic variants was performed in 22 patients using Sanger sequencing, following DNA isolation.
Results: Seventy patients were diagnosed with CPP, of which 62(88.5%) were female and 8(11.5%) were male. The mean age of symptom onset was 7.1 years for girls and 5.7 years for boys, with the mean age at diagnosis being 7.8 years and 5.9 years, respectively. The mean age of the patients in whom the mutations were investigated was 7.8 years. Genetic analysis revealed no pathogenic MKRN3 variants. The rs2239669 variant, classified as benign, was detected in 11 heterozygous and in one patient in homozygous form.
Conclusion: The detection of only a benign variant in MKRN3, with no pathogenic variants identified, may be attributed to the absence of a positive family history in all patients and the relatively higher mean age of the cohort. A limitation of this study is the small number of patients analyzed genetically and the inability to assess other genes related to central precocious puberty.

Keywords: Early puberty, central precocious puberty, *MKRN3* gene

Öz

Amaç: Santral erken puberte (SEP), hipotalamus-hipofiz-gonad aksının erken yaşta aktive olmasıyla ortaya çıkan bir tablodur ve kız çocuklarında daha sık görülmektedir. MKRN3 mutasyonları gibi bazı genetik faktörler tanımlanmış olsa da, bu faktörlerin SEP gelişimindeki rolü hâlâ tam olarak aydınlatılamamıştır. Bu çalışmada, *MKRN3* geninin santral erken puberte gelişimindeki rolü araştırılmıştır.
Gereç ve Yöntem: Çalışmaya, santral erken puberte tanısı almış 70 hasta dâhil edildi. Hastaların demografik bilgileri, antropometrik ölçümleri ve laboratuvar verileri dosya kayıtlarından elde edilmiştir. *MKRN3* genindeki patojenik varyantları belirlemek amacıyla, DNA izolasyonu yapılan 22 hastaya Sanger sekanslama yöntemiyle genetik analiz uygulanmıştır.
Bulgular: Çalışmaya dâhil edilen 70 hastanın 62'si (%88,5) kız, 8'i (%11,5) erkekti. Belirti başlangıç yaşı kızlarda ortalama 7,1 yıl, erkeklerde ise 5,7 yıl olarak belirlendi. Tanı yaşı ortalama olarak kızlarda 7,8 yıl, erkeklerde ise 5,9 yıl olarak saptandı. Genetik analiz yapılan hastaların ortalama yaşı 7,8 yıldı. Yapılan genetik analiz sonucunda, *MKRN3* geninde patojenik varyanta rastlanmadı. Benign olarak sınıflandırılan rs2239669 varyantı, 11 hastada heterozigot ve 1 hastada homozigot olarak saptandı.
Sonuç: *MKRN3* geninde yalnızca benign bir varyantın saptanması ve patojenik varyantların bulunmaması, çalışmaya dâhil edilen hastaların hiçbirinde aile öyküsünün olmaması ve hasta grubunun ortalama yaşının görece yüksek olmasıyla ilişkili olabilir. Çalışmanın başlıca kısıtlılıkları, genetik analiz yapılan hasta sayısının sınırlı olması ve santral erken puberte ile ilişkili diğer genlerin değerlendirilememesidir.

Anahtar kelimeler: Erken ergenlik, santral erken puberte, *MKRN3* geni

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INTRODUCTION

Puberty is a period of rapid growth during which reproductive functions are acquired and gender development is complete. The hypothalamus-pituitary-gonadal axis controls both puberty and reproductive functions through stimulatory and inhibitory mechanisms[1]. The hypothalamic–pituitary–gonadal axis (HPG) is active during the fetal period. It becomes inactive at birth but is reactivated immediately afterwards, causing an increase in gonadotropin hormones in the plasma[2]. After six months, the level of gonadotropin hormones decreases, and HPG does not become active until puberty[3]. The HPG axis is regulated by both the negative and positive feedback mechanisms. It has been reported that neuropeptides, such as kisspeptin, neurokinin B, and dynorphin (KNDy), released from the arcuate nucleus in the hypothalamus, affect the HPG axis[4]. GnRH is released from gonadotroph cells in the anterior pituitary gland and stimulates the synthesis and release of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Gonadotropins stimulate the release of sex hormones from the gonads by acting on follicle cells in the ovaries and Leydig cells in the testes. Puberty begins with thelarche in girls and an increase in testicular volume in boys[5,6]. Pubertal changes were staged according to the Tanner scala[7].

The timing of puberty has decreased, particularly in developed countries. The onset of puberty before the age of 8 years in girls and 9 years in boys was defined as precocious puberty. This was approximately 20 times more common among the girls [8]. Central precocious puberty (CPP) occurs due to the premature activation of the hypothalamic-pituitary-gonadal axis. Organic causes were more common in boys than in girls. Hypothalamic hamartomas are the most common organic lesion[9]. Excessive consumption of processed chemicals in cosmetics, sedentary lifestyle, and obesity can cause precocious puberty. Recent studies have suggested a possible association between excessive omega-3 intake and the development of precocious puberty; however, further research is required to clarify this potential link[10].

The importance of genetic influences on the timing of puberty has recently increased. Genes reported to be associated with CPP include *KISS1, MKRN3, and DLK1*[11,12]. Macorin ring finger protein 3 (MKRN3) is an inhibitor of the hypothalamic–pituitary–gonadal axis. Loss-of-function mutations in *MKRN3* cause CPP[11]. *MKRN3* was first identified by Jong et al[13]. Abreu et al also reported that *MKRN3* gene mutation in patients with CPP and they found three frameshift mutations in 5 patients with familial CPP[14]. Approximately 50 genetic variants have been identified to date.

In light of previous studies reporting *MKRN3* mutations in familial cases of CPP, we hypothesized that *MKRN3* variants might also contribute to the etiology of sporadic cases. By retrospectively evaluating a cohort of patients diagnosed with CPP, this study aimed to assess the presence of *MKRN3* variants and to characterize the clinical features of these patients. Although no pathogenic variants were detected, our findings highlight the potential impact of family history and age at presentation on the likelihood of detecting *MKRN3* mutations.

MATERIALS AND METODS

Sample and procedure

This retrospective study evaluated patients diagnosed with CPP between 2002 and 2017 at Cukurova University, and 70 patients with consistent follow-up were included in the analysis. Patient records were maintained according to standard hospital protocols, and data reliability was ensured through review by experienced pediatric and endocrinology specialists. Inclusion criteria included patients with a confirmed pubertal response to GnRH testing. Exclusion criteria were peripheral precocious puberty and incomplete records. A total of 84 patients were considered, of whom 14 were excluded due to missing data. Sociodemographic findings, age at symptom onset, diagnosis, physical examination findings, body mass index (BMI), laboratory and radiological findings, and the height of the parents were recorded. This study was approved by the Ethics Committee of Cukurova University (Approval No: 63, dated April 14, 2017). Patients with CPP who had a pubertal response to GnRH testing were included in this study. Bone age was evaluated using the Greulich and Pyle Atlas, which estimates skeletal maturity by comparing hand and wrist radiographs with standardized reference images. Pubertal staging was assessed according to the Tanner and Marshall scale, which classifies breast development in girls, genital development in boys, and pubic hair development in both sexes from stage 1 to 5. In addition, testicular volume (assessed by Prader orchidometer) and axillary hair development were also recorded[15]. All evaluations were performed by two experienced pediatric endocrinologists, and discrepancies were resolved by consensus.

Laboratory analysis

Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E2) were measured at the Hospital Laboratory of the Cukurova University of Medicine. LH and FSH levels were measured using an immunochemiluminescence (ICMA) method. The GnRH stimulation test involved taking basal LH, FSH, estradiol, and testosterone levels, followed by intravenous administration of 2.5 mcg/kg of GnRH intravenously. FSH, LH, estradiol, and testosterone levels were measured 0, 30, 45, and 60 min after GnRH administration. The LH assay has a detection limit of 0.1 IU/l. We considered stimulated LH levels greater than 5 IU/l and/or a stimulated LH/FSH ratio greater than 0.66 to indicate the start of the pubertal period [9].

Genetic analysis

Due to limited resources, only MKRN3 was analyzed in this study, which represents a limitation. Genetic analysis was performed in 22 patients, as some parents declined to provide consent for genetic testing. A physical examination of the patients was performed, detailed histories were obtained, and the study form was completed. Blood samples (2 ml blood sample were collected from the patients into an EDTA tube and stored at +4°C throughout the study. Informed consent was obtained from all the patients and/or their parents. A silica-based commercial kit (10023; Qiagen) was used to isolate DNA. Primers covering the coding regions of MKRN3 and adjacent areas were obtained using Primer3 (https://primer3.ut.ee/). Relevant gene regions were amplified in patients by process, and sequence analysis was performed using an Applied Biosystems 3130 Genetic Analyzer. The results obtained were read using the Sequencher DNA sequence analysis program and the peak images were interpreted.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 23.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were used, and continuous variables are presented as mean ± standard deviation or median (minimum–maximum), according to the distribution of the data.

RESULTS

Demographic findings

Seventy patients were diagnosed with CPP. Of these, 62 (88.5%) were female and eight (11.5%) were male. The female-to-male ratio was 7.7:1. The most common presenting complaint in girls was breast development (57.8%), whereas pubic hair growth (75%). The mean age at symptom onset in the female patients was 7.1 years, and the mean age at diagnosis was 7.8 years. The mean bone age was 9.4 years. The mean weight SDS of the female patients was 1.14, mean height SDS was 1.08, and mean BMI SDS was 0.83. Sixteen women (25.8%) of the female patients were overweight. The mean target height was 159.9 cm and the target height SDS was -0.5. The mean predicted adult height was 158.4 cm. The mean growth velocity was 3.2 cm over six months (Table 1).

For the male patients, the mean age at symptom onset was 5.7 years and the mean age at diagnosis was 5.9 years. The mean bone age was 7.4 years. The mean weight SDS for male patients was 1.69, mean height SDS was 0.95, and mean BMI SDS was 1.46. The mean target height was 163.2 cm and the target height SDS was -0.86. The mean predicted adult height was 166.2 cm. The growth velocity was 3.54 cm over six months (Table 2). The mean age of cases investigated for mutations in our study was 7.8 years

Laboratory findings

In female patients, the mean FSH level was 4.63 IU/L, LH level was 2.93 IU/L, E2 level was 25.3 pg/ml, and testosterone was 0.1 ng/ml. Of the 35 patients whose results were available, the median GnRH-stimulated peak LH level was 22.9 IU/L, FSH level was 15.2 IU/L, and LH/FSH ratio was 1.52. In male patients, the mean FSH level was 1.23 IU/L, LH level was 1.68 IU/L and testosterone was 3.2 ng/ml, the median GnRH stimulated peak LH level were 14.2 IU/L.

Molecular findings

Genetic analysis of *MKRN3* was performed in 22 patients diagnosed with CPP and no pathogenic variants were found in any patient. In 11 patients, a variant resulting from a change in the cytosine (C) nucleotide to thymine (T) nucleotide at the 663rd base position of *MKRN3* (NM_005664), leading to a synonymous codon change of the 221st amino acid proline (c.663C>T;p. Pro221=) was identified as heterozygous in one patient and homozygous in another. The total allelic frequencies of the rs2239669 variant in the gnomAD database were 0.2759 and 0.2857 in the Turkish population (Kars et al., 2021). The variant, evaluated online using the InterVar classification system (https://wintervar.wglab.org/), was predicted to be benign according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) criteria, with a classification of BA1, BS1, BP4, and BP7.

Table 1. Demographic and anthropometric findings in female patients

Variable	Mean	Median (Min-Max)
Age at diagnosis	7.8	8 (1,7-10.8)
Age at symptom onset	7.1	7.5 (1-10.7)
Bone age	9.4	10 (1-13)
Weight SDS	1.14	0.99 (-2.04-3.91)
Height SDS	1.08	1.08 (-2.53-7.14)
BMI SDS	0.83	0.84 (-1.21-2.94)
Target height SDS	-0.5	-0.33 (-2.78-0.43)
Mean growth velocity	3.2	3.1 (2.0-5.3)

BMI: Body Mass İndex, SDS: Standard Deviation Score, Min: minimum, Max: maximum

Table 2. Demographic and anthropometric findings in male patients

Variable	Mean	Median (Min-Max)
Age at diagnosis	5.9	6.9 (1.4-9.3)
Age at symptom onset	5.7	6.4 (1.2-9.0)
Bone age	7.4	8 (2-12.5)
Weight SDS	1.69	2.14 (-1.67-3.69)
Height SDS	0.95	1.44 (-2.18-3.96)
BMI SDS	1.46	1.7 (-0.13-2.94)
Target height SDS	-0.86	-0.92 (-2.27-0.59)
Mean growth velocity	3.54	3.65 (2-4.5)

BMI: Body Mass İndex, SDS: Standard Deviation Score, Min: minimum, Max: maximum

DISCUSSION

Precocious puberty is defined as the onset of puberty before the age of eight in girls and nine in boys. It can also be defined as secondary sexual maturation occurring at an age of more than two standard deviations below the mean for the general population[16]. It is more prevalent in girls than boys. In most studies, the prevalence in girls was found to be between 86% and 92%[17,18,19]. In our study, 90% of the patients were female, which is consistent with previous studies. In contrast to girls with central precocious puberty (CPP), where 90% of the cases are idiopathic, the prevalence of organic central nervous system (CNS) lesions is notably higher in boys, ranging from 40% to 90%[9,20,21]. In our study, organic CNS lesions were observed in five female patients (8%) and one male patient (12.5%). Despite the limited number of male patients, this rate was higher, which is consistent with findings in the literature.

In the study of Kim et al. in 2017, the age of diagnosis of patients with CPP was 7.62±0.46 years, in the study of Ying et al. it was 7.1±0.75 years, and in a study conducted in China in 2016, the age of diagnosis was 7.8 years[22,23,24]. In many studies, the age of diagnosis has been reported to be between 6-8.5 years of age[18,25,26,27]. The mean age at diagnosis in our study was also consistent with the literature

It has been reported that the rate of body fat accumulation is directly proportional to the rate of pubertal development, and childhood obesity may cause early puberty[28-32]. The BMI was > 2 SDS in 16 (22.8%) female CPP patients. Similar studies conducted in 2016 found that the mean weight SDS was 0.7 ± 0.8, and the mean BMI SDS was 0.4 ± 1.0. In our study, 27.7% of the patients were overweight or obese[33].

Bone age is an important parameter in the evaluation and diagnosis of CPP, as it often progresses faster than chronological age in affected patients. The mean bone age was 9.4 years in female and 7.4 years in male, as determined in the present cohort. In the study of Leger et al., bone age was 8.4±0.5, in the study of Ying et al. it was 10.6±0.53, in the study of Kim et al [22,23,27]. The difference between the bone age and calendar age (delta BA-CA) in patients with CPP was 1.51. The difference between the bone age and calendar age (delta BA-CA) in patients with CPP was 1.51 years. Therefore, patients with CPP have higher bone age than their calendar age. This finding is consistent with those in the literature[34,35].

Genetic factors affect age at puberty. Recently, the genes that cause CPP have been identified. *MKRN3*, which is encoded on chromosome 15, is one of the most common genes. Abreu et al. detected three frameshift mutations in five of 15 familial CPP cases[14]. Şimşek et al. detected 2 heterozygous frameshift mutations in Turkey in 2016[36]. In a study by Kırkgöz et al. in 2023, pathogenic variants were detected in three of 102 patients diagnosed with CPP[37]. In our study, the presence of *MKRN3* mutations was investigated in 22 patients diagnosed with CPP, and no pathogenic variants were detected in any of the patients. However, 11 patients carried the rs2239669 (c.663C>T; p. Pro221=) variant heterozygous, whereas one patient carried it homozygous. The common occurrence of the rs2239669 variant in the population after allele frequency checks in the gnomAD database (0.2766) also supported the presumption that the variant is benign. Additionally, no significant difference was found between the patients with rs2239669 (c.663C>T; p. Pro221 =) variant than in other patients. In a study conducted by Jeong et al. in 2017, *MKRN3* was examined in 26 cases of CPP; however, no mutations were detected, in line with our own findings[38]. Two heterozygous variants were identified in this study. One of these variants was identical to the rs2239669 variant (c.663C>T; p. Pro221) that was also detected in our patients. In a similar study, the rs2239669 variant was reported in three out of 13 patients diagnosed with CPP, and its association with early puberty in males was suggested, whereas no relationship was found with CPP in females[39]. A study by Ortiz-Cabrera et al. claimed that although this variant is silent against the protein amino acid chain, it could lead to protein degradation by affecting gene expression or posttranslational properties[40]. However, this functional interpretation remains speculative and should be considered as the author's opinion in the absence of confirmatory functional studies. The average age of patients screened for mutations in our study was 7.8.

The age range of cases of CPP with an MKRN3 mutation, as found in many studies, is 3.0–6.5 years for females and 5.9–9.7 years for males[14,41,42,43,44]. In the study by Jeong et al., similarly our study, the mean age at diagnosis was 8.05 ± 1.14 years in girls and 9.37 ± 0.82 years in boys[38]. In a study by Pagani et al., the variant was found in 6 of 19 patients, and the average age at diagnosis was higher, similar to our study [39]. The higher average age in our study suggested that *MKRN3* mutations may cause CPP to begin at an earlier age. Similarly, Simon et al. found that girls with *MKRN3* mutations started puberty at a younger age than females without pathogenic variants[45]Pathogenic variation of the *MKRN3* gene appears to be particularly common (in up to 33–46% of cases) in families with a history of the condition[45,46]. None of the patients who underwent the genetic analysis had a family history. This may explain why no pathogenic variants were detected in this study.

The limitations of this study include the small number of patients evaluated for genetic factors and the inability to examine genes other than MKRN3. These limitations may have restricted the generalizability of our findings and prevented the identification of additional genetic contributors to CPP. Nevertheless, our results highlight the importance of incorporating genetic assessment into clinical practice, particularly for patients presenting with suggestive clinical features or a positive family history. Future studies with larger cohorts and multigene panels may further enhance diagnostic accuracy and inform individualized treatment strategies for CPP.

In conclusion, CPP is becoming increasingly prevalent, and accurate diagnosis is essential for timely initiation of treatment. Genetic correlation with the onset of puberty is becoming more significant and could be a valuable marker for early diagnosis. Future research should focus not only on expanding cohort sizes and using multigene panels but also on integrating genetic findings with clinical, hormonal, and environmental data to build comprehensive risk models.

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