RESEARCH ARTICLE / *Araştırma Makalesi*

Pineal Cysts in Children with Precocious Puberty: Is It a Coincidental Finding?

Erken Puberte Tanılı Olgularda Saptanan Pineal Kistler: Tesadüfi Bir Bulgu mu?

Saliha Ciraci[1], Recep Polat[2]

[1] Pediatric Radiology, Department of Radiology, Sakarya University Training and Research Hospital, Sakarya, Turkey
[2] Pediatric Endocrinology, Department of Pediatrics, Sakarya University Training and Research Hospital, Sakarya, Turkey

Yazışma Adresi / *Correspondence:*
Saliha Ciraci

Department of Radiology, Sakarya University Training and Research Hospital, Sakarya, Turkey
T: **+90 506 367 24 36** E-mail **: atasaliha@hotmail.com**

Geliş Tarihi / Received : **28.01.2022** Kabul Tarihi / Accepte: **16.06.2022**

Orcid :

Saliha Ciraci https://orcid.org/: 0000-0002-3680-9368
Recep Polat https://orcid.org/0000-0002-3786-0739

(Sakarya Tıp Dergisi / *Sakarya Med J* 2022, 12(2):315-321) DOI: 10.31832/smj.1060348

Abstract

Objective	The aim of this study is to assess the correlation between precocious puberty and pineal cysts in children.
Materials and Methods	In this case-control study, brain MR scans of 122 patients with precocious puberty and 122 children in the control group were evaluated for the presence and size of pineal cysts. Pineal cysts were assessed as true cyst and cystic transformation in terms of their sizes. The presence of pineal cysts/cystic transformation was compared between the two groups. In the precocious puberty group, the baseline and peak LH levels of patients with pineal cyst, cystic transformation and without cyst-cystic transformation were compared.
Results	The chi-square test indicated no significant correlation between precocious puberty and pineal cyst and between precocious puberty and pineal cystic transformation (p=0.2537 and p=0.8797 respectively). There was no significant difference in the basale and peak LH levels between the patients with pineal cyst, cystic transformation and without cyst-cystic transformation in the precocious puberty group (p=0.566 and p= 0.367 respectively).
Conclusion	According to the results of the present study, there was no correlation between pineal cysts and precocious puberty. Therefore, it is a correct approach to accept pineal cysts detected in MR scans as an incidental finding in cases with precocious puberty.
Keywords	precocious puberty; pineal gland; melatonina; magnetic resonance imaging

Öz

Amaç	*Bu çalışmanın amacı, çocuklarda erken puberte ile pineal kistler arasındaki ilişkinin değerlendirilmesidir.*
Gereç ve Yöntemle	*Bu vaka-kontrol çalışmasında erken puberte tanılı 122 olgu ve kontrol grubu 122 çocuğun beyin MR görüntüleri pineal kist varlığı ve boyutları açısından değerlendirildi. Pineal kistler boyutlarına göre gerçek kist ve kistik transformasyon olarak ayrıldı. Erken puberte ve kontrol grubu pineal kist/kistik transformasyon varlığı açısından karşılaştırıldı. Erken puberte grubunda pineal kist saptanan, kistik transformasyon saptanan ve kist/kistik transformasyon saptanmayanların pik ve bazal LH değerleri karşılaştırıldı.*
Bulgular	*Ki-kare testi ile erken puberte ile pineal kist arasında ve erken puberte ile pineal kistik transformasyon arasında anlamlı ilişki saptanmadı (sırasıyla p=0,2537ve p=0,8797). Erken puberte grubunda kist/kistik transformasyon izlenmeyen, kistik transformasyon saptanan ve kist saptananlar arasında pik ve bazal LH değerleri açısından anlamlı farklılık bulunmadı (sırasıyla p=0,566 ve p=0,367).*
Sonuç	*Çalışmamızın sonuçlarına göre, pineal kistler ile erken puberte arasında herhangi bir ilişki saptanmamıştır. Bu nedenle, erken puberte tanılı olgularda MR incelemelerde saptanan pineal kistlerin insidental bulgu olarak kabul edilmeleri doğru bir yaklaşımdır.*
Anahtar Kelimeler	*erken puberte; pineal bez; melatonin; manyetik rezonans görüntüleme*

INTRODUCTION

Precocious puberty refers to puberty beginning before age 8 in girls and before age 9 in boys.[1] Precocious puberty is divided into 2 main groups; central precocious puberty (true/gonadotropin-dependent) and peripheral precocious puberty (false/gonadotropin-independent). Central precocious puberty develops by the activation of stimulatory systems on gonadotropin releasing hormone (GnRH) neurons.[2]

Congenital central nervous system (CNS) lesions (Chiari malformation, hydrocephalus, arachnoid cyst, hypothalamic hamartoma, myelomeningocele), acquired CNS lesions (tumors such as glioma, ependymoma, pinealoma and craniopharyngioma, hypoxic ischemic encephalopathy, irradiation, traumatic injury, bleeding, infection), genetic mutations, chromosomal abnormalities and idiopathic precocious puberty are among the causes of central precocious puberty.[3,4]

The control mechanisms that onset puberty are still undiscovered. The phenomenon that induces puberty is thought to be an increase in the amplitude and quantity of GnRH secretory bursts by the hypothalamic neurons that produce GnRH.[5]

Precocious puberty is associated with tumors that are located in the sellar, suprasellar and pineal regions.[6] The etiology of precocious puberty in some of CNS tumors is known to be directly associated with the production of GnRH or human chorionic gonadotropin (hCG) by the lesions or the secretion of neuroactive substances that stimulate the release of GnRH through the neighborhood. The etiology is unknown in some of tumors.[6-8]

Only germ cell tumors that secrete hCG induce precocious puberty among pineal tumors.[9] Additionally, in the literature some authors have reported cases of pineal cysts considered to be associated with precocious puberty.[10-12]

Experimental evidence suggests that the pineal gland has functions in the neuroendocrine control of puberty in animals.[13-15] There have been studies reporting that the pineal gland affects reproductive function at the hypothalamic and gonadal levels in humans, but the hypothesis that the pineal gland controls sexual maturation could not be confirmed.[16-18]

Pineal cysts are one of the pathologies that can be found during cranial magnetic resonance (MR) scans in radiology practice and are typically regarded as an incidental finding. A value of 5 mm is considered as the lower limit of true cysts. Pineal cysts between 2-5 mm are considered as cystic transformation of the gland.[19] We examined the correlation between pineal cysts/cystic transformation and precocious puberty based on the cases of the pineal cyst - precocious puberty described in the literature and as well as the thesis of the effects of melatonin on sexual maturation.

The aim of this study is to assess the frequency of pineal cysts in children for whom cranial magnetic resonance images (MRIs) were taken due to precocious puberty and to compare them with the control group. Furthermore, it is aimed to compare gonadotropin levels of patients with and without a pineal cyst/cystic transformation in the precocious puberty group.

MATERIALS and METHODS

Ethical considerations, patients and study design

This retrospective study was approved by the ethics committee of Sakarya University (approval date/number: 30.06.2021-39909). Images from 122 children for whom brain MRIs were taken for precocious puberty and 122 children who had brain MRIs for screening between January 2015 and December 2020 were analyzed retrospectively. Precocious puberty and control groups consisted of children with similar F/M ratio, mean age and body mass index (BMI). The control group constituted the patients who applied to pediatric outpatient clinics and requested

MR imaging for screening. The exclusion criteria were hydrocephalus, tumor, hypoxic ischemic encephalopathy and other pathologies that might cause precocious puberty and neurological/oncological diseases.

Imaging procedures and analysis of data

MR imaging was performed in our hospital with a 1.5 T Siemens MR device (Signa, Voyager; GE Healthcare, WI, USA). The MR examination included the following sequences:

- a. Coronal and axial T2-weighted fast spin echo (FSE) pulse sequence (TR/TE, 5404 ms/ 87 ms; matrix, 192×192; slice thickness, 3 mm),
- b. Axial fluid-attenuated inversion recovery (FLAIR) pulse sequence (TR/TE, 7640 ms/ 87 ms; matrix, 132×256; slice thickness, 3 mm),
- c. Coronal, axial and sagittal three dimension (3D) T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) pulse sequence (TR/TE, 1500 ms/ 2.58 ms; matrix, 179×224; slice thickness, 1 mm).

A pediatric radiologist with 13 years of experience in radiology analyzed the images. The presence of pineal cysts and the size of the cysts were recorded both in the precocious puberty and control groups. True pineal cysts (diameters more than 5 mm) and cystic transformations (diameters ranging from 2 to 5 mm) were assessed separately. The precocious puberty group was divided into three groups based on the presence of pineal cyst, the presence of cystic transformation and the absence of cyst-cystic transformation. Precocious puberty patients' basale and peak luteinizing hormone (LH) levels were recorded.

Statistical Analysis

SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to conduct statistical analyses. Numerical data were expressed as mean and standard deviation (SD), whereas categorical data were expressed as frequency and percentage. The chi-square test was employed to investigate the correlation between precocious puberty and pineal cysts. The Kruskal-Wallis test was used to assess the correlation between the presence of cysts/cystic transformation and hormone levels in patients with precocious puberty. The value of $p< 0.05$ was accepted as statistically significant. A post hoc power analysis was performed using a web-based application developed by Inonu University to ensure that adequate power was present to interpret the data.

Table 1. Comparison of the pineal cyst /cystic transformation between precocious puberty and control group with chi-square test.

Pineal lesion	Precocious puberty group	Control group	p
Pineal cyst (n, %)	13 (10.65%)	8 (6.55%)	0.2537
Pineal cystic transformation (n, %)	28 (22.95%)	29 (23.77%)	0.8797

RESULTS

The study included 122 patients who were examined for precocious puberty and 122 children for whom MRIs were taken for screening as a control group . The F/M ratios in the precocious puberty and control groups were 118/4. The precocious puberty and control groups had similar mean ages (7.98±1.26 vs 8.03±1.31) ($p= 0.392$). No significant difference was also found between the precocious puberty and control groups in terms of BMI (17.71±2.71 vs 16.01±3.32) ($p> 0.05$).

True pineal cysts were identified in 13 (10.65%) patients of the precocious puberty group and 8 (6.55%) patients of the control group (Image 1). The chi-square test indicated no significant correlation between precocious puberty and pineal cyst ($p= 0.2537$). (Table 1)

Pineal cystic transformations were identified in 28 (22.95%) patients of the precocious puberty group and 29 (23.77%) patients of the control group (Image 2). The chi-square test also indicated no significant correlation between precocious puberty and pineal cystic transforma-

tion (p= 0.8797). (Table 1)

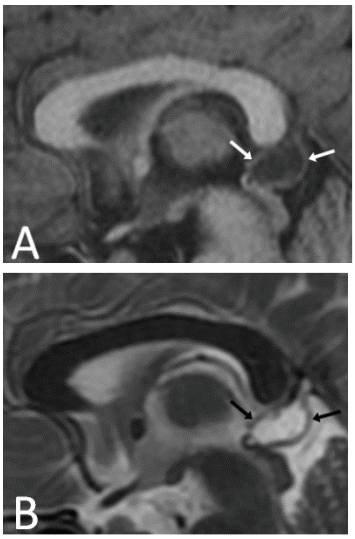

Figure 1. On MR imaging, a true pineal cyst (A) which appears hypointense in T1-weighted sagittal sequences and (B) hyperintense in T2-weighted sagittal sequences.

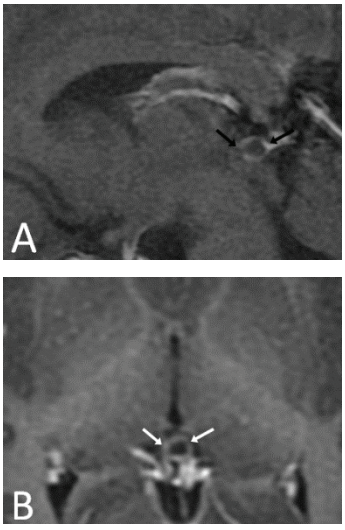

Figure 2. On MR imaging, a pineal cystic transformation which appears hypointense (A) in post-contrast T1-weighted sagittal sequences and (B) in post-contrast T1-weighted axial sequences.

The basale LH values were determined as 1.27±1.75, 1.41±1.62 and 1.76±1.61 and peak LH values were determined as 11.92±10.82, 7.8±5.02 and 12.70±8.17 respectively in precocious puberty patients with pineal cyst, with cystic transformation and without cyst-cystic transformation. The basale and peak LH values revealed no statistically significant difference among the three groups (p= 0.566 and p= 0.367 for basale LH and peak LH respectively) (Image 3,4).

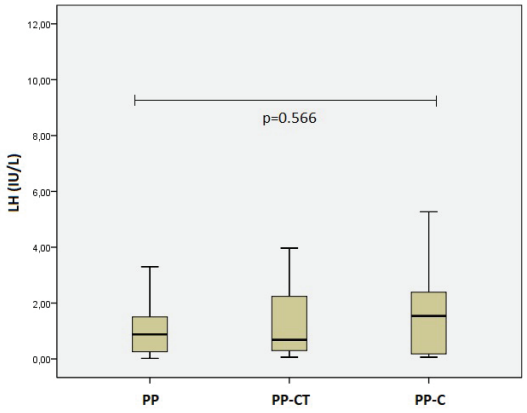

Figure 3. A graph of the distribution of basale LH levels in the precocious puberty group. The cases were divided into subgroups; PP, precocious puberty without pineal cyst/cystic transformation; PP-CT, precocious puberty with pineal cystic transformation and PP-C, precocious puberty with pineal cyst.

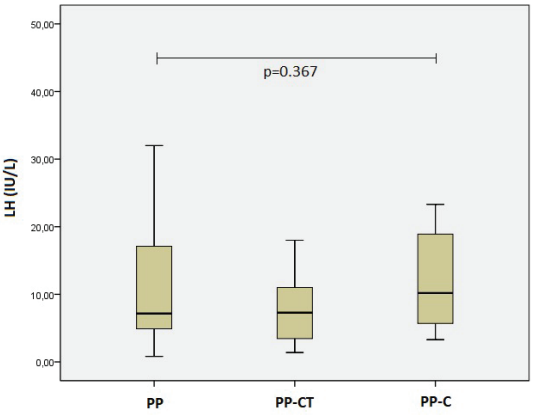

Figure 4. A graph of the distribution of peak LH levels in the precocious puberty group. The cases were divided into subgroups; PP, precocious puberty without pineal cyst/cystic transformation; PP-CT, precocious puberty with pineal cystic transformation and PP-C, precocious puberty with pineal cyst.

DISCUSSION

There have been studies reporting that the pineal gland affects human reproductive function both at the hypothalamic-pituitary level by inhibiting the hypothalamic pulsatile secretion of the hormone that releases gonadotropin and at the gonadal level via melatonin receptors.[16,17] However, no literature study has been conducted on the correlation between precocious puberty and pineal cysts. In a study, V. Lacroix-Boudrioua et al. examined 56 cases of precocious puberty and 116 cases of idiopathic short stature (ISS) for pineal cysts and identified pineal cysts in 10.7% of precocious puberty cases and 11.2% of ISS patients. However, the age, gender and other characteristics were not similar in both groups in this study. This research was designed to identify the prevalence of pineal cysts in children who had MR imaging and there was also no comparison between the two groups. To our knowledge, our study is the first attempt to investigate the correlation between precocious puberty and pineal cysts. We identified true pineal cysts in 10.65% of the precocious puberty group and 6.55% of the control group. Similar rate of pineal cysts in the precocious puberty group indicated in the study by V. Lacroix-Boudhrioua et al. was supportive for results of our current research.[19]

The prevalence of pineal cysts has been reported to range from 1.5% to 10.8% in various studies.[20] However, in these studies pineal cysts were not differentiated as true pineal cysts and cystic transformations. In the present study, we examined pineal cysts by dividing into two groups; true pineal cysts and pineal cystic transformations. In a study, in which brain MR scans of 14,516 patients under the age of 25 were examined and 5 mm was considered as the baseline of cyst diameter, the rate of the pineal cyst was found to be 2.0%. In this study, the highest prevalence was found in the girls between the ages of 6 and 12 (3.7%). The cause of this group's high rate was unknown.[21] In another study, pineal cysts were found ranging in size from 1.5 to 16 mm in 57% of children and it was reported that cysts were more prevalent in girls.[22] There was a wide range in the incidence of pineal cysts in the literature. Our study did not represent the true incidence of the pineal cysts in children because the patients were involved in the age range of 6 to 10 years and predominantly girls.

The hypothalamic-pituitary-gonadal axis, which is inactive until the age of ten years, is activated by an increase in the amplitude and frequency of GnRH pulses and puberty begins.[23] The main phenomenon that induces puberty is assumed to be an increase in the amplitude and quantity of GnRH secretory bursts by the hypothalamic neurons that produce GnRH.[5] Precocious puberty is known to be associated with tumors that are located in the pineal and sellar regions.[6] Pineal tumors secreting hCG cause precocious puberty.[9] Besides, we found three case reports asserting that there may be a relationship between pineal cysts and precocious puberty.[10-12] Also, experimental evidence suggest that the pineal gland has function in the neuroendocrine control of puberty in animals.[13-15] In the present study, we compared precocious puberty and control groups with similar gender distribution, age and BMI and found no difference in the presence of pineal cysts between the two groups. Based on this result, we concluded that pineal cysts identified in MR scans of precocious puberty patients should be accepted as an incidental finding.

Some studies on headache/migraine patients reported that pineal cysts may play role in the etiology of the disease by reduction in melatonin levels due to disruption in circadian melatonin secretion.[24-28] In these researches, the authors referenced to the studies indicating low melatonin levels in patients with headaches/migraines in the literature. Similarly, it has been suggested that pineal gland pathologies and decreased melatonin may play role in the etiology of precocious puberty.[18] However, no studies have conducted on the association between precocious puberty and pineal cysts except case reports. On the other hand, Holanda et al. assessed the sleep duration and melatonin levels in children with precocious puberty. They found that melatonin levels were lower in precocious puberty patients than in

prepubertal children with normal growth and they asserted that melatonin may have antigonadotropic efficiency.[29] In the present study, we compared the gonadotropin values of the patients with and without pineal cyst in the precocious puberty group. The patients with pineal cyst had slightly higher baseline and peak LH values, but there was no statistically significant difference. This result cast doubt on the hypothesis asserting that decreased melatonin levels lead to increase in gonadotropins. We believe that even if melatonin has antigonadotropic activity, this activity is most probably weak and does not affect pubertal development.

The first limitation of our study was the lack of melatonin values in puberty and control groups, as it was retrospective. Another limitation was the absence of LH values in the control group. Prospective studies which include melatonin and LH values of subjects may yield more detailed and precise results. Sample size was found to be inadequate with post hoc power analysis. Therefore, another limitation was the insufficient number of patients in this study.

CONCLUSION

Consequently, studies in the literature asserting that pineal cysts may cause precocious puberty are limited to case reports and animal experiments. Our findings suggest that pineal cysts identified in the MR imaging should be accepted as an incidental finding and not be associated with precocious puberty. However, there is still need for research on the effect of pineal gland and its pathologies on puberty since the etiopathogenesis of puberty has not been properly clarified and factors that might affect pubertal development are multiple.

This retrospective study was approved by the ethics committee of Sakarya University (approval date/number: 30.06.2021-39909).

Conflict of Interest: The authors declare no conflict of interest related to this work and do not have any financial relationship with the organization that sponsored the research.

References

1. *Long D. Precocious Puberty. Pediatr Rev 2015;36:319-321.*
2. *Fahmy JL, Kaminsky CK, Kaufman F, Nelson Jr MD, Parisi MT. The radiological approach to precocious puberty. Br J Radiol 2000;73:560-567.*
3. *Soriano-Guillén L, Argente J. Central precocious puberty, functional and tumor-related. Best Pract Res Clin Endocrinol Metab 2019;33:101262.*
4. *Topaloglu AK, Turan I. Genetic Etiology of Idiopathic Hypogonadotropic Hypogonadism. Endocrines 2022;3:1-15.*
5. *Ojeda SR, Lomniczi A, Mastronardi C, Heger S, Roth H, Parent AS, et al. Minireview: the neuroendocrine regulation of puberty: is the time ripe for a systems biology approach? Endocrinology 2006;147:1166e74.*
6. *Rivarola G, Belgorosky A, Mendilaharzu H, Vidal G. Precocious puberty in children with tumours of the suprasellar and pineal areas: organic central precocious puberty. Acta Paediatr 2001; 90:751-756.*
7. *Cnossen MA, Stam EN, Cooiman LC, Simonsz HJ, Stroink H,Oranje AP, et al. Endocrinologic disorders and optic pathway gliomas in children with neurofibromatosis type I. Pediatrics 1997;100:667–670.*
8. *Judge DM, Kulin HE, Santen R, Page R, Trabucki S. Hypothalamic hamartoma: a source of luteinizing-hormone-releasing factor in precocious puberty. N Engl J Med 1977;296:7–10.*
9. *Fetell MR, Stein BM. Neuroendocrine aspects of pineal tumors. Neurol Clin 1986;4:877-905.*
10. *Dickerman RD, Stevens QE, Steide JA, Schneider SJ. Precocious puberty associated with a pineal cyst: is it disinhibition of the hypothalamic-pituitary axis? Neuro Endocrinol Lett 2004;25:173-175.*
11. *Benítez Fuentes R, Velázquez de Cuéllar, Paracchi M, Blanco Rodríguez M, Soriano Guillén L. Central precocious puberty and pineal gland cyst: an association or incidental finding? Ann Pediatr (Barc) 2008;68:72-73.*
12. *Kumar KV, Verma A, Modi KD, Rayudu BR. Precocious puberty and pineal cyst: an uncommon association. Indian Pediatr 2010;47:193-194.*
13. *Ramaley JA, Bunn EL. Seasonal variations in the onset of puberty in rats. Endocrinology 1972;91:611-613.*
14. *Aubert ML, Rivest RW, Lang U, Winiger BP, Sizonenko PC. Delayed sexual maturation induced by daily melatonin administration eliminates the LH response to naloxone despite normal responsiveness to GnRH in juvenile male rats. Neuroendocrinology 1988;48:72-80.*
15. *Buchanan KL, Yellon SM. Delayed puberty in the male Djungarian hamster: effect of short photoperiod or melatonin treatment on the GnRH neuronal system. Neuroendocrinology 1991;54:96-102.*
16. *Wishoff JH, Epstein F. Surgical management of symptomatic pineal cysts. J Neurosurg 1992;77: 896-900.*
17. *Macchi MM, Bruce JN. Human pineal physiology and functional significance of melatonin. Front Neuroendocrinol 2004;25:177-195.*
18. *Aleandri V, Spina V, Morini A. The pineal gland and reproduction. Hum Reprod Update 1996;2:225-235.*
19. *Lacroix-Boudhrioua V, Linglart A, Ancel PY, Falip C, Bougnères PF, Adamsbaum C. Pineal cysts in children. Insights Imaging 2011;2:671-678.*
20. *Choy W, Kim W, Spasic M, Voth B, Yew A, Yang I. Pineal cyst: a review of clinical and radiological features. Neurosurg Clin N Am 2011;22:341-351.*
21. *Al-Holou WN, Garton HJL, Muraszko KM, Ibrahim M, Maher CO. Prevalence of pineal cysts in children and young adults. J Neurosurg Pediatr 2009;4:230-236.*
22. *Whitehead MT, Oh CO, Choudhri AF. Incidental pineal cysts in children who undergo 3-T MRI. Pediatr Radiol 2013;43:1577-1583.*
23. *Sizonenko PC. Physiology of puberty. J Endocrinol Invest 1989;12:59-63.*
24. *Seifert CL, Woeller A, Valet M, Zimmer C, Berthele A, Tölle T,et al. Headaches and pineal cyst: a case-control study. Headache 2008;48:448-452.*
25. *Ciraci S, Kalın S, Genç HM, Kutlubay B, Oysu A, Bükte Y. Evaluation of the relationship between pineal cyst and childhood headache with MR Imaging. Neurology Asia 2021;26:113-116.*
26. *Waldenlind E, Gustafsson SA, Ekbom K, Wetterberg L. Circadian secretion of cortisol and melatonin in cluster headache during active cluster periods and remission. J Neurol Neurosurg Psychiatry 1987;50:207-213.*
27. *Claustrat B, Loisy C, Brun J, Beorchia S, Arnaud JL, Chazot G. Nocturnal plasma melatonin levels in migraine: A preliminary report. Headache 1989;29:242-245.*
28. *Alehan FK. Value of neuroimaging in the evaluation of neurologically normal children with recurrent headache. J Child Neurol 2002;17:807-809.*
29. *Holanda FS, Tufik S, Bignotto M, Maganhin CG, Vieira LHL, Baracat EC, et al. Evaluation of melatonin on the precocious puberty: a pilot study. Gynecol Endocrinol 2011;27:519-523.*