

ORIGINAL PAPER

doi: 10.5455/medarch.2019.73.101-103

MED ARCH. 2019 APR; 73(2): 101-103

RECEIVED: FEB 12, 2019 | ACCEPTED: APR 01, 2019

¹Department of Endocrinology, Bahrami Pediatrics Hospital, Tehran University of Medical Sciences, Tehran, Iran

²Department of Pediatrics, School of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran

Corresponding author: Dr. Zahra Soheilrad, Assistant Professor, Sabzevar Heshmatie Hospital, Sabzevar University of Medical Sciences, Sabzevar, Iran. Tel.: +985144651300. E-mail: soheilz2@medsab.ac.ir, ORCID ID: <http://orcid.org/0000-0003-3419-191X>

The Influence of Gonadotropin-Releasing Hormone Agonist Treatment on Thyroid Function Tests in Children with Central Idiopathic Precocious Puberty

Fariba Naderi¹, Zahra Soheilrad², Zahra Haghshenas¹

ABSTRACT

Introduction: In recent years, the treatment of idiopathic central precocious puberty using gonadotropin-releasing hormone agonist (GnRH) agonist has been considered as a common treatment. To date, there is not much information about the effect of GnRH agonist treatment on pediatric thyroid function. **Aim:** The aim of this study was to evaluate the influence of GnRH treatment on thyroid function tests in children with central idiopathic precocious puberty. **Material and Methods:** This cross-sectional study investigated 50 children with idiopathic precocious puberty treated with GnRH agonist, who were referred to Bahrami pediatric hospital, Tehran, Iran. Patients' height, weight, and symptoms of hypothyroidism were evaluated every two months. Thyroid function tests, T4 and thyroid-stimulating hormone (TSH), were reviewed every 6 months. Data were analyzed using SPSS Statistics, Version 18. **Results:** The majority of the children who participate in this study were female. 72% of children with central idiopathic precocious puberty had a significant increase in TSH level ($P=0.002$). In this group of patients, 66% and 6% had subclinical and clinical increases in thyroid function tests, respectively. The estimated time to thyroid dysfunction was 12.37 months. It is found that only 2% of patients showed thyroid dysfunction during the first 6 months of the treatment. **Conclusion:** The results of this study showed that more than 70% of children who were undergoing GnRH agonist treatment for central precocious puberty had impaired thyroid function (especially subclinical hypothyroidism). Therefore, evaluating thyroid function in children with precocious puberty who are under treating with GnRH agonist, would be reasonable; especially one year after initiating the treatment.

Keywords: Puberty, Precocious; Gonadotropin-Releasing Hormone; Hypothyroidism.

1. INTRODUCTION

Central precocious puberty is a form of precocious puberty, which becomes evident with the early puberty of the hypothalamus-pituitary glandular axis (1). Central precocious puberty is mostly idiopathic and is more common in girls (1-3). For these patients, medicinal treatments can be beneficial in a variety of ways and, on the other hand, may have detrimental effects on their health. Treatment with the gonadotropin-releasing hormone agonist (GnRH) agonist is a healthy, relatively old treatment (4). Most of the complications of this treatment are manifested as pseudo-menopausal in children (5). However, thyroid hormones disorders are considered to be the complications of treatment with the GnRH agonist which has been neglected in pediatric studies, and

is mostly studied in adults and cases other than precocious puberty (6).

2. AIM

Due to the paucity of information in this regard in the literature, the aim of this study was to investigate the influence of GnRH agonist treatment on thyroid function tests in pediatric patients with central idiopathic precocious puberty.

3. METHODS

This cross-sectional study was conducted in Bahrami pediatric hospital, Tehran, from May to December 2012. After obtaining approval from the institutional Ethics Committee and getting informed consent from participants or their surrogate decision maker, 50 children with central idiopathic precocious puberty were selected. In the current study for

© 2019 Fariba Naderi, Zahra Soheilrad, Zahra Haghshenas

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

confirming the diagnosis of idiopathic central precocious puberty, imaging, clinical and laboratory criteria were evaluated and matched (3). Diagnostic criteria for early idiopathic central precocious puberty included: 1) Secondary changes during puberty before age 8 years for girls and before age 9 years for boys, 2) Bone age > length age > chronological age, 3) baseline Estrogen levels > 9p-gr/dl in girls and testosterone levels between 20-1200 ngr/dl 4) Luteinizing Hormone (LH) level ≥ 0.6 , Follicle stimulating hormone (FSH) ≥ 2 , 5) Post GnRH (after 1 hour) > 4.2 IU/L, 6) normal Dehydroepiandrosterone (DHEA S) level for that age and greater than length age.

All patients had normal brain magnetic resonance imaging (MRI). At the beginning of study, the thyroid function tests results were normal for these children and all of their family members were healthy. None of the children had a history of certain diseases such as diabetes, hyperlipidemia and congenital *adrenal hyperplasia*, and were not treated with any medicines.

The data from this study was completed by the researcher in certain referrals. All of these children were examined every two months in terms of their height, weight and hypothyroidism symptoms. Moreover, thyroid function tests including T4 and thyroid stimulating hormones (TSH) were performed every 6 months by a special laboratory. All patients finished their treatment and participated in all periodic visits. Data were analyzed by SPSS, Version 18. The P values less than 0.05 was considered statistically significant.

4. RESULTS

Among all 50 children treated with the GnRH agonist, 86% were female. The mean age of precocious puberty in boys and girls were 8.7 and 7.2 years, respectively. While 57% and 42% of the boys had pubis hairs growth and orchitis, respectively, 44% of the girls had bigger clitoris and pubis hairs growth as the first manifestations of the puberty. Symptoms related to puberty in children are summarized in Table 1.

Variables	Girls (%)	Boys (%)
Aggressive behaviors	79	100
Sweating	51	29
Bone pain	44	57
Sleep disorders	25	14
Irritability	23	14

Table 1. Signs of precocious puberty in both genders

Moreover, 46% of children had advanced bone age and only 34% had normal bone age compared to their chronological age. The mean age difference was significantly higher in girls than boys (0.36 vs. 0.34), which was not statistically significant ($P=0.49$). Considering the body mass index (BMI) less than 18.5, as a criteria for underweight, 33% of girls were underweight, and only one child was obese (BMI > 25). It has been revealed that 20% and 46% of children had a lower and higher bone age compared to their real chronological age, respectively. In the thyroid function test, 72% of all children had

impaired thyroid function test and a significant increase in their TSH level were observed ($P=0.002$) (Figure 1).

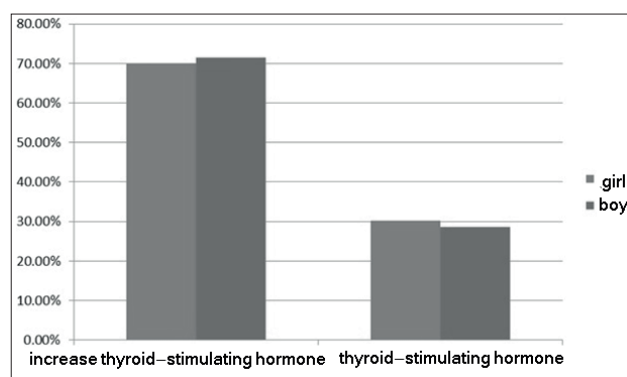


Figure 1. Comparison of the percentage of children with increase thyroid stimulation in comparison with those who had normal levels of hormone along with considering their genders

It was found that 66% and 6% of children showed a subclinical and clinical increases in thyroid function test, respectively. The estimated mean time to occurrence of impaired thyroid function test was 12.37 months. Only 2% of the children showed thyroid dysfunction in the first 6 month of their life.

5. DISCUSSION

Precocious puberty is defined as the occurrence of changes during puberty before the age of 8 years for girls and 9 years for boys (1-2). The present study indicated that in our region, the puberty rate for girls and boys is 7 and 8 years, respectively. Given that the age of puberty is different in each area, the Berberoglu study reported a variable ratio of central precocious puberty in two sexes (male to female respectively) from 3 to 1, to 23 to 1 (1). In the current study, girls' dominance in this ratio over boys was also observed. Among every six girls, one male had central idiopathic precocious puberty. Despite the fact that most girls had bone pain and sweating during precocious puberty and boys reported bone pains, the incidence of violent behavior was very tangible in both sexes. Precocious puberty has always been a stressful topic, concerning families and healthcare personnel. This problem includes child sexual abuse, in addition to puberty-related growth impairments (7). Rapid bone maturation, unconventional physical appearance among peers and being short in the future, along with behavioral and personality disorders associated with precocious puberty are considered as important complications of this disease (1). Therefore, the treatment of this disease has always been a concern for families and healthcare providers. Treatment with the GnRH agonist for central precocious puberty has been used from 20 years ago (4). This treatment delayed the menarche and increased the child' height (4, 8). The final height would increase by the injection of subcutaneous GnRH agonist every 6 weeks. In some studies, a grater increases in children's height, with rhGH injection, has been reported (9). This treatment would have reversible changes to BMI, reproductive system and bone density (10); although it would not result in decreasing the bone quality and quantity

after menarche (11-12). Patients treated with the GnRH agonist may report vaginal bleeding for 3 to 5 days, especially 2 weeks, after initiating the treatment (5). Moreover, increased appetite was observed in children who were treated with the GnRH agonist (13). In addition to these complications, changes in thyroid hormones levels have been reported in other cases of the use of the GnRH agonist. The use of the GnRH agonist can lead to an immune rebound and consequently could lead to autoimmune thyroid disorders (14). Some cases of thyroid disorder have been reported in adults after a GnRH agonist treatment (14-15).

This study has some limitations. The small sample size was a limitation of the study; other studies with larger sample size are recommended. Also, due to the nature of cross-sectional studies, it is difficult to discern causal relationships; therefore, further well design studies are warranted to confirm this finding.

6. CONCLUSION

The results of this study showed that more than 70% of children who were undergoing GnRH agonist treatment for central precocious puberty had impaired thyroid function (especially subclinical hypothyroidism). Therefore, evaluating thyroid function in children with precocious puberty who are under treatment with GnRH agonist, would be reasonable; especially one year after initiating the treatment.

- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms.
- **Author's contributions:** F.N., Z.S. and ZH. gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. Each author had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Conflicts of interest:** There are no conflicts of interest.
- **Financial support:** This study has been financially supported by the deputy of research and technology, Tehran University of Medical Sciences, Tehran, Iran.

REFERENCES

1. Berberoğlu M. Precocious Puberty and Normal Variant Puberty: Definition, etiology. *J Clin Res Pediatr Endocrinol*. 2009; 1(4): 164-174. doi: 10.4274/jcrpe.v1i4.3.
2. Bridges N, Christopher J, Hindmarsh P, Brook C. Sexual precocity: sex incidence and aetiology. *Arch Dis Child*. 1994; 70(2): 116-118.
3. Sultan C, Gaspari L, Kalfa N, Paris F. Clinical expression of precocious puberty in girls. *Endocr Dev*. 2012; 22: 84-100. doi: 10.1159/000334304.
4. Carel JC, Lahlou N, Roger M, Chaussain JL. Precocious puberty and statural growth. *Hum Reprod Update*. 2004; 10(2): 135-147. doi: 10.1093/humupd/dmh012
5. Li WJ, Gong CX, Guo MJ, Xing J, Li T, Song WH, et al. Efficacy and safety of domestic leuporelin in girls with idiopathic central precocious puberty: a multicenter, randomized, parallel, controlled trial. *Chin Med J (Engl)*. 2015; 128(10): 1314-1320. doi: 10.4103/0366-6999.156773.
6. Li PI, Li Y, Yang CL. Gonadotropin releasing hormone agonist treatment to increase final stature in children with precocious puberty: a meta-analysis. *Medicine (Baltimore)*. 2014; 93(27): e260. doi: 10.1097/MD.0000000000000260.
7. Tremblay L, Frigon J-Y. Precocious puberty in adolescent girls: a biomarker of later psychosocial adjustment problems. *Child Psychiatry Hum Dev*. 2005; 36(1): 73-94. doi: 10.1007/s10578-004-3489-2.
8. Anik A, Catli G, Abaci A, Bober E. Effect of gonadotropin-releasing hormone agonist therapy on body mass index and growth in girls with idiopathic central precocious puberty. *Indian J Endocrinol Metab*. 2015; 19(2): 267-271. doi: 10.4103/2230-8210.131770.
9. Liang Y, Wei H, Li J, Hou L, Zhang J, Wu W, et al. Effect of GnRHα 3.75 mg subcutaneously every 6 weeks on adult height in girls with idiopathic central precocious puberty. *J Pediatr Endocrinol Metab*. 2015; 28(7-8): 839-846. doi: 10.1515/jpem-2014-0305.
10. Pasquino AM, Pucarelli I, Accardo F, Demiraj V, Segni M, Di Nardo R. Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin-releasing hormone analogs: impact on adult height, body mass index, bone mineral content, and reproductive function. *J Clin Endocrinol Metab*. 2008; 93(1): 190-195. doi: 10.1210/jc.2007-1216.
11. Iannetta R, Melo AS, Iannetta O, Marchini JS, Paula FJ, Martinelli CE, et al. Use of a Gonadotropin-releasing Hormone Analog to Treat Idiopathic Central Precocious Puberty Is Not Associated with Changes in Bone Structure in Postmenarchal Adolescents. *J Pediatr Adolesc Gynecol*. 2015; 28(5): 304-308. doi: 10.1016/j.jpag.2014.09.002.
12. Alessandri SB, Pereira Fde A, Villela RA, Antonini SR, Elias PC, Martinelli CE, Jr., et al. Bone mineral density and body composition in girls with idiopathic central precocious puberty before and after treatment with a gonadotropin-releasing hormone agonist. *Clinics (Sao Paulo)*. 2012; 67(6): 591-596.
13. Kim YJ, Lee HS, Lee YJ, Lim JS, Kim SY, Kim EY, et al. Multi-center clinical trial of leuprolide acetate depot (Luphere depot 3.75 mg) for efficacy and safety in girls with central precocious puberty. *Ann Pediatr Endocrinol Metab*. 2013; 18(4): 173-178. doi: 10.6065/apem.2013.18.4.173.
14. Han EJ, Song HD, Yang JH, Park SY, Kim SH, Yoon HK, et al. Thyroid dysfunction associated with administration of the long-acting gonadotropin-releasing hormone agonist. *Endocrinol Metab (Seoul)*. 2013; 28(3): 221-225. doi: 10.3803/EnM.2013.28.3.221.
15. Eyal O, Rose SR. Autoimmune thyroiditis during leuprolide acetate treatment. *J Pediatr*. 2004; 144(3): 394-396. doi: 10.1016/j.jpeds.2003.11.036