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Short Communication

GnRH test for the diagnosis of central precocious puberty: is it time to revisit the protocol ?

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Introduction

Early activation of the hypothalamic-pituitary-gonadal axis may cause central precocious puberty (CPP), that is, the occurrence of sexual development before 8 yr in girls and 9 yr in boys (1). Idiopathic early maturation of the entire hypothalamic-pituitary-gonadal axis is more frequent in females, whereas organic disorders, such as tumors of the central nervous system, are more frequently involved in CPP in males (2). To date, there is no univocal opinion about the most appropriate diagnostic test to confirm or rule out this condition, although its diagnosis is based on the full spectrum of physical and hormonal changes of puberty, largely suspected on a clinical basis and confirmed by specific blood tests, including basal hormone dosage, radiological assessments, and dynamic tests, such as the GnRH test, which reveals activation of the hypothalamic-pituitary-gonadal axis (1, 2). Such crucial tests are regularly performed by intravenous infusion of up to 100 μg of GnRH, followed by serial doses of LH and FSH at 0, 30, 60, 90, and 120 min (3). Although this test is considered the gold standard for diagnosis, there are important variations in the LH cutoff used: Italian guidelines suggest a cutoff of 3.3 or 5 IU/L (3), while international societies suggest a cutoff of up to 10 IU/L (4). This hormonal variability under stimulation confirms the complexity of this diagnostic procedure, which requires a significant duration (up to 120 min after GnRH administration), peripheral venous access, and serial blood sampling, with a risk of complications, including allergic reactions. This study aimed to evaluate whether a simplified GnRH test could be a valid alternative to the traditional GnRH test for the diagnosis of CPP.

Materials and Methods

We analyzed the results of GnRH tests performed at the Pediatric Endocrinology Day Hospital of the Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome to determine the optimal single blood sampling time for assessing LH peaks in patients with suspected CPP and to evaluate the feasibility of performing a simplified test to establish a diagnosis of CPP. In particular, we analyzed a total of 46 GnRH tests, performed between January 2019 and July 2022; for each test, we obtained data referred to the serial dosages of LH at 0, 30, 60, 90, and 120 min, evaluating the frequency of LH peaks and the possible final diagnosis of CPP (**Table 1**). We considered 'diagnostic' a result of LH equal to or above 3.3 IU/L, as usually considered at our center.

For LH measurements, a serum sample of at least 1 mL was used. Hemolyzed or lipemic samples were discharged. FSH and LH appear to be stable in the serum for 8 days at room temperature; in our hospital, they are usually analyzed within 5–7 days. The immunoassay analysis at our hospital meets the national quality standards and complies with the Joint Commission International (JCI) rules.

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Table 1. Characteristics of the GnRH tests in children with a suspicion of central precocious puberty

	Study population (n = 46)	Central precocious puberty (n = 27)	Negative test (n = 19)
Median age (yr), SDS (yr),	5.96 (3.91)	5.64 (2.70)	5.53 (0.89)
Age range (yr)	1.02–7.96	1.02–7.96	1.28–7.93
Females, n (%)	44/46 (95.65%)	27/27 (100%)	17/19 (89.47%)
Median LH value (IU/L), SDS (IU/L)	9.04 (7.19)	15.55 (9.22)	1.24 (0.63)
LH peak at 30 min n (%)	30/46 (65.22%)	23/30 (76.67%)	7/30 (23.33%)
LH peak at 60 min, n (%)	12/46 (26.09%)	3/12 (25%)	9/12 (75%)
LH peak at 90 min, n (%)	3/46 (6.52%)	1/3 (33.33%)	2/3 (66.67%)
LH peak at 120 min, n (%)	1/46 (2.17%)	0/1 (0%)	1/1 (100%)

Results

Almost all GnRH tests were performed in girls (n = 44, 95.65%) with a median age of 5.96 yr, while only two boys were tested (7.3 and 7.8 yr old). A CPP diagnosis was confirmed in 27 cases (58.69%, all girls) and excluded in 19 (41.31%). Among the 46 patients, in 30 (65.22%), 12 (26.09%), three (6.52%), and one (2.17%) case(s), the LH peak was reached 30, 60, 90, and 120 min after the administration of GnRH, respectively. Separately analyzing 27 cases with a confirmed diagnosis of CPP, the LH peak was reached in 23 children (85.19%) at 30 min, in three cases (11.11%) at 60 min, and in one case (3.7%) at 90 min. The combined use of two single samples at 30 and 60 min was concordant with the final result of the complete GnRH test in 26 of the 27 cases of confirmed CPP (96.3%). Therefore, in our cohort of children suspected of having CPP, LH measurements at 30 min after GnRH infusion and the combined test with LH measurements at 30 and 60 min maintained an accuracy like that for the classic complete test.

Discussion

Although our observations were limited to a small cohort of pediatric patients, several studies have confirmed these results. For example, Choi *et al*. analyzed a group of 1,958 children, of whom 1,232 had a subsequently confirmed diagnosis of CPP, and demonstrated that the combined hormonal dosage at 45 and 60 min from the start of the GnRH test showed a sensitivity of 99.1% and a specificity of 100% in identifying the LH peak for all children, suggesting a possible reduction in blood sampling during the GnRH test (5). Similar results were reported by Cao *et al*., who studied 1,492 children with suspected CPP and suggested the possibility of a single blood sample at 60 min and showed that even the basal LH dosage, when higher than a certain cutoff (above 0.535 mIU/L), could be used to diagnose CPP without a stimulus test (6). Kim *et al*. suggested a single dose 30 min after GnRH administration to identify a diagnostic LH peak, which was consistent with our observations (7). The GnRH test remains the diagnostic gold standard in cases of suspected CPP, and its interpretation as well as the methods of performance can be reevaluated, simplifying the execution of the test, reducing the number of blood samples, and integrating results of the partial test with clinical and anthropometric data, as described by Yeh *et al*. (8).

Conclusion

The use of a simplified GnRH test with a single dose of LH assessed 30 min after GnRH administration represents a valid alternative to the traditional test. Although cost optimization and higher facilities for children are important clues, further confirmatory studies with larger populations will help confirm the effectiveness of our results.

Conflict of interests: The authors declare that they have no disclosure in relationship with the subject of this communication.

References

1. Aguirre RS, Eugster EA. Central precocious puberty: From genetics to treatment. Best Pract Res Clin Endocrinol Metab 2018;32: 343–54. [Medline] [CrossRef]
2. Soriano-Guillén L, Argente J. Central precocious puberty, functional and tumor-related. Best Pract Res Clin Endocrinol Metab 2019;33: 101262 [CrossRef]. [Medline]
3. Bangalore Krishna K, Fuqua JS, Rogol AD, Klein KO, Popovic J, Houk CP, *et al*. Use of gonadotropin-releasing hormone analogs in children: update by an International Consortium. Horm Res Paediatr 2019;91: 357–72. [Medline] [CrossRef]
4. Miranda-Lora AL, Torres-Tamayo M, Zurita-Cruz JN, Aguilar-Herrera BE, Calzada-León R, Rivera-Hernández AJ, *et al*. Diagnosis of precocious puberty: clinical guideline for the diagnosis and treatment of precocious puberty. Bol Méd Hosp Infant México 2020;77(Supl 1): 7–14 (in Spanish). [Medline]

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5. Choi R, Kwon A, Oh Y, Lee SG, Lee EH. Time points for gonadotropin-releasing hormone stimulation test results in Korean children. J Clin Med 2021;10: 252. [Medline] [CrossRef]
6. Cao R, Liu J, Fu P, Zhou Y, Li Z, Liu P. The diagnostic utility of the basal luteinizing hormone level and single 60-minute post GnRH agonist stimulation test for idiopathic central precocious puberty in girls. Front Endocrinol (Lausanne) 2021;12: 713880. [Medline] [CrossRef]
7. Kim HK, Kee SJ, Seo JY, Yang EM, Chae HJ, Kim CJ. Gonadotropin-releasing hormone stimulation test for precocious puberty. Korean J Lab Med 2011;31: 244–9. [Medline]
8. Yeh SN, Ting WH, Huang CY, Huang SK, Lee YC, Chua WK, *et al*. Diagnostic evaluation of central precocious puberty in girls. Pediatr Neonatol 2021;62: 187–94. [Medline] [CrossRef]