Hormonal changes throughout puberty in congenital hypogonadotropic hypogonadism and Pump indication

Xiaoya Ren (renxya2014@163.com)
Beijing Children's Hospital

Yuanyuan Tian
Beijing Children's Hospital

Guoshuang Feng
Beijing Children's Hospital

Yi Wang
Beijing Children's Hospital

Beibei Zhang
Beijing children hospital

Bingyan Cao
Beijing children's hospital

Jiajia Chen
Beijing children's hospital

Chunxiu Gong
Beijing children's hospital

Research

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Abstract

Background It is difficult to capture the exact time of pubertal initiation in normal children, including the detailed patterns of physical development, the cut-off values of hormone changing at pubertal initiation and maturation.

Method Patients diagnosed with CHH were included in to prospectively investigate the hormones changes by GnRH pulsed pump therapy. We investigate testis volume and the hormones of HPG axis at basal and LHRH stimulated at 0 and the end of week 1, 4, and 12. Receiver operating characteristic (ROC) curve was plotted to determine the cut-off values of pubertal hormones.

Results: Twenty-four CHH patients received pulse LHRH therapy were rolled in this study. stimulated FSH reached peak and LH increased significantly at week4. At this time point we workup the cut-off hormones values for pubertal initiation by ROC. They are: basal LH 1.32 IU/L, LH/FSH 0.34, the stimulated LH 4.45 IU/L and LH/FSH 0.54 for initiation. Basal INH-b elevated at week1, followed by T at week4, then AMH decreased at week12 coupled with testicle and penis growth. the pituitary response of CHH is normal when LH in the range of 1.81-3.17 IU/L and the LH / FSH in the range of 0.57-0.87.

Conclusion we got the cut-off values of puberty initiation: basal LH 1.32 IU/L, stimulated LH 4.45 and LH/FSH 0.54 signed HPG axis activated. we got the cut-off hormones values of normal pituitary response: stimulated LH in the range of 1.81-3.17 IU/L and LH / FSH in the range of 0.57-0.87.

Introduction

It is difficult to capture the exact time of initiation of puberty in normal children, such as when breasts in girls and testicles in boys begin to grow, especially in boys. As a result, research on the detailed patterns of physical development during puberty and the cut-off values and changes of hormones at initiation of puberty and developmental maturation is rare. It is generally believed that hormonal changes during puberty are a direct result of the stimulating effect of luteinizing hormone (LH) on initiation of puberty (1; 2); thus, LH is widely accepted as an indicator to evaluate initiation of puberty. However, researchers haven't yet to reach an agreement on the cut-off value of LH, especially in boys. The previous reference value was based on inquiries regarding signs and symptoms and laboratory tests on blood samples. For example, information on when breasts begin to develop in girls (at approximately 10 years of age), when testicle volume begins to increase in boys (at 11.5 years of age), and the age of initial menstruation in girls and seminal emission in boys are obtained through inquiry instead of observation. Hence, the data provide a time frame (time interval), rather than a time point, and it is difficult to quantify the time frame. Therefore, the exact time of initiation of puberty is uncertain when it is determined based on the initial onset of secondary sexual characteristics or growth spurts or serum hormone levels (3). As a result, it is difficult to determine precise cut-off values for initiation of puberty from previous studies (4,5). Moreover, the reference cut-off values for initiation of puberty vary greatly between boys and girls (6), theoretically, the values of boys and girls should be similar. Is this difference due to gender differences? Or is it

because the onset of puberty in boys is more difficult to detect, leading to the delay of the measured time point?

Although it is not easy to detect initiation of puberty in boys, it is easy and precise to determine testicle volume and penis length (7). Testosterone (T) level is usually concordant with changes in secondary sexual characteristics in boys, whereas the link between oestrogen level and physical changes is weak in girls. It is more reliable and practical to investigate Tanner staging and T levels to determine and identify puberty in boys (7).

Some recent studies have shown that besides LH and follicle-stimulating hormone (FSH), anti-Mullerian hormone (AMH) and inhibin B (INH-B) are also involved in the initiation of puberty (11; 12). Hence, a series of hormonal changes are responsible for initiating puberty; however, systematic research on these changes is lacking. Therefore, in this study, we recruited congenital hypogonadotropic hypogonadism (CHH) patients to be a model to prospectively study the initiation and developing of their puberty with exogenous GnRH, getting the physical characteristics and hormones changes during the induction of puberty and to determine the cut-off values of hormones in the HPG axis during three stages: initiation, development, and maturation. GnRH pump therapy is safe and effective; but it is important to determine whether pump therapy is indicated for patients with pituitary disorders. We further discussed the pump treatment indication of CHH.

Materials And Methods

1.
Subjects and methods
1.1
Male Kallmann's syndrome (KS)/congenital hypogonadotropic hypogonadism (CHH) patients were included in this study to prospectively investigate the puberty onset and hormones changes during Beijing Children's Hospital between January 2008 and March 2017.
1.2
Inclusion and exclusion criteria for KS/CHH patients

Inclusion criteria (13):

 Pre-puberty (Tanner I or testicle volume < 4 mL), with or without olfactory abnormalities; patients must older than 12 yrs and have small penis and/or cryptorchidism; bone age > 12 years; karyotype 46XY, SRY (+); no increase in Testosterone level after LHRH test at baseline; serum Testosterone level ≤ 20 ng/mL after LHRH test at baseline; and no hypothalamus or pituitary mass per imaging studies.

Exclusion criteria:

 Unwilling to sign the informed consent; systemic diseases; and hypergonadotropic hypogonadism.

1.
1.3 Clinical data: (1) They were examined at baseline and followed-up at weeks 1 ± 1 day, 4 ± 2 days, and 12 ± 2 days after treatment, then followed up every 3 months till 12 months. An increased Testosterone when testicle volume was greater than 3 ml was used as the indicator for initiation of puberty. (2) Data collection: height, weight, body mass index (BMI), PL and testicle volume, biochemistry, hormones; (4) LHRH stimulation test(15);
2.
1.4 Protocol for GnRH pump pulse therapy (13):8–10∝ g of GnRH (200∝ g/mL) was injected every 90 minutes with a pump. If any side effects occurred or T > 500 ng/dl, the dose of GnRH was reduced accordingly.
3.
1.5 ROC curve:

Receiver operating characteristic (ROC) curve was used to determine the cut-off hormones value at the initiation of puberty, which were used to evaluate the time points of initiation, development, maturation. The area under the curve (AUC) was used to identify the cut-off value. A cut-off value of hormone had a diagnostic value when the AUC was greater than 0.8 and $p < 0.05$. A value with a certain level of sensitivity and specificity was used as the cut-off value. HPG axis initiation was considered when a relationship between LH and T was established, so the ROC curve plotted when approximately 50% of the patients showed an HPG initiating. Maturation was considered when feedback of the HPG axis was established and GnRH reached the peak and no longer rising.

1.6 Statistical analysis

This was a prospective cohort study in which sex hormones levels were compared before and after continuous LHRH pulse therapy. GraphPad Prism v5 was used to plot curves. SPSS v17.0 was used for statistical analysis. Repeated measures analysis of variance was performed to analyse hormonal changes at different time points before and after treatment in the same patient.

1.7. Determination of hormone levels

A MAGLUMI® 2000 instrument was used to perform radioimmunoassay to determine the levels of T.

A Roche e601 instrument was used to perform chemiluminescence assays to determine the levels of LH, FSH, AMH and INH-B.

1.8. The study was approved by the ethics committee of Beijing Children’s Hospital, which acts in compliance with ethical standards defined by the Declaration of Helsinki. Written consent for research purposes was provided by all participants and their parents or legal guardians.

Results

1. General information

A total of 24 patients with HH (KS17) were included in this study. The average age at first visit was 14.01 ± 1.40 years; the bone age was ≥ 12, at Tanner I. Fifteen patients (62.5%) had a small penis, others had small penis and cryptorchidism. All 24 patients completed 4 weeks and 18 patients completed 12 weeks study.

2. Hormones profiles during pump therapy

Basal hormones profiles

After treatment, FSH and INH-B began to rise at week 1, with no changes in T, AMH levels or testicle volume. LH started increasing with a significant increase combined with T level at the end of week4, but no changes in testicle volume or AMH. At W12, LH and INH-B continued to rise, but FSH stopped increasing at a high level, testosterone could be detected and the testicle volume was greater than 3 ml since then, while, AMH began to decrease (Detailed values in Table 1 and figure 1).

LHRH stimulation test (15)

LH peaked at 30 minutes and FSH at 60 minutes after LHRH stimulation. We take values at these 2 points respectively to study ROC.

Stimulated Hormones Profiles

Stimulated LH did not rise until week 4, but FSH increased significantly at week 1 and stabilized by week 4. LH/FSH ratio decreased at week 1, began to increase at week 4, and stabilized at week12. Testosterone began to rise at week 4. These results indicated that puberty was initiated by week 4, and developmental maturation was achieved by week12. No significant change was observed in AMH, or INH-B. (Detailed values in Table 1, Fig. 1)

3. Changes in physical characteristics during pump therapy

No reported body changes but After 12 weeks of pump therapy, patients reported testicle and penis growth, especially testicle volume, which increased more significantly and earlier than penis size (Table 1). Moreover, beard or pubic hair appeared in 38.9% and 3 patients reported initial seminal emission after 39 weeks treatment.

4. ROC curve of hormone levels (detailed in Table 2, Table 3)

At week 4, basal LH continued to rise and T levels rose in 12 patients with significant positive correlation with LH levels ($r = 0.736$, $p < 0.01$). Therefore, week 4 was used as the puberty ignition time point for the ROC curve. Week 4 was used as the positive group and week 0 as the negative group to plot the ROC curve to determine the cut-off values of T, LH, LH/FSH, and INH-B before and after the stimulation.

When basal LH > 1.32 IU/L in all patients, T level elevated in 65% patients (13/20) and LH/FSH > 0.34. The cut-off basal LH and LH/FSH were 1.32 IU/L and 0.34 respectively. At the same time we got the cut-off value of stimulated LH was 4.45 IU/L. The corresponding ROC curve showed that the cut-off value of LH/FSH after stimulation was 0.54. Similarly, the cut-off value of INH-B was 54.5 pg/mL at the initiation of puberty.

At week 12 of treatment, FSH stabilized, INH-B continued to rise, and T levels increased, indicating that when week 12, patients went into maturation. The ROC curve analyses of T, LH, LH/FSH, and INH-B at week 12 are shown in Table 3.

Compare to the published reference of girl's stimulated LH 3-5 IU/L and LH/FSH 0.6 as the HPG activating indicator (6), this study on boys showed a similar cut-off values, that is LH at 4.45 IU/L and LH/FSH 0.54 in boys at week4(initiation) ($p=0.139$; $p=0.406$). So were similar with those stimulated LH 4.92 IU/L and LH/FSH 0.69 at week 12(maturation).

5. Further follow-up

Overall, follow-up data indicated normal testicles in most cases. Sixteen patients continued to receive continuous gonadorelin pump therapy after 12 weeks, of them 8 patients treated>1 year; 3 patients experienced seminal emission at month 9, month 17, and month 24, respectively. The first patient experienced seminal emission at age 17; however, continued treatment of his testicles stopped development when reached 8 ml, then increasing the dose, his testicles continued development. For the second patient, his testicles contracted once pump therapy was discontinued, so retreat him with pump again. For both patients, sperm testing indicated low sperm motility within the 1 month of spermache. One patient felt his daily-life affected because of increased erections (> 3 times/day) at month 6; thus, the dose was reduced to one-third of original dose.

Discussion

Many factors are involved in the initiation of puberty, which is a result of the interaction between multiple neural nuclei in the brain and hypothalamic neuroendocrine cells and is subject to the effects of environmental and metabolic factors (8–10; 13; 16). It is a challenge to investigate puberty because it is not easy to capture the exact puberty initiation time individually. Continuous LHRH pituitary pulse therapy of CHH patients mimics the process of puberty. This prospective study with highly homogeneous

patients, regularly sample and physical data taking, assured the results reliable. We got the initiation-developing-maturation anthropometry and cut-off values of each phase provided a useful reference for the diagnosis of early and delayed puberty.

1. The hormones basal and stimulated profiles and the cut-off values of initiation of the HPG axis and puberty

At week 1, INH-B rose and followed by LH and FSH (Fig. 1). LH/FSH decreased first then climbed up until testosterone increase at last means puberty ignition. Therefore, the decrease in stimulated LH/FSH (0.37 to 0.26) and the increase in INH-B preceded puberty. The continued LH increase followed by an increase in LH/FSH was the most significant marker of initiation of puberty. Basal LH1.32 IU/L and 3.54 IU/L are the cut off values of puberty starting and maturation. Before real initiation of puberty, a decrease in LH/FSH was followed by a continued LH increase and stabilized FSH, suggesting that Sertoli cells mature before Leydig cells, and sperm was produced after both Sertoli and Leydig cells reached maturation, thereafter seminal emission was the final milestone of developmental maturation.

Some studies on hormone levels at different Tanner stages have shown somewhat different values from this study (17–19). We consider the previous studies were cross-sectional descriptive study, whereas this was a prospective longitudinal study of hormone levels, which reflected dynamic changes in hormone levels. Therefore, the results of this study are more precise and reliable.

The cut-off values in this study were similar to the reference values of girls (6), suggesting no significant difference in cut-off values of hormone levels for the initiation of puberty between boys and girls. This study also compared the starting and maturing stages of HPG levels of hormones with adult reference (20), no significant difference were shown. It is suggested that once the feedback HPG axis was activated, there are no significant differences in hormones after stimulation.

Basal LH 1.32 IU/L and LH/FSH 0.34 have high sensitivity and can enable the timely detection of early puberty. For male patients considered to be with delayed puberty when around 14 years old, if their LH level is close to these values indicate constitutional delay of growth and puberty (CDGP), and any values below these cut-off values suggest HH. The 2015 Chinese expertise consensus on the diagnosis and treatment of IHH states that IHH should be considered if basal LH is 0-0.7 IU/L, and delayed puberty or partial IHH should be considered if LH is ≥ 0.7 IU/L(21). Moreover, the 2016 Chinese expert consensus on the diagnosis and treatment of IHH states that LH ≥ 1 IU/L indicates preliminary treatment response to pump therapy for 3 days in IHH patients (3; 22). Our research of ROC have given a recommendation cut-off value of LH 1.32 IU/L for initiation of puberty, which is closed to the consensus and higher than that in the consensus, it means a higher specificity of our study. We also noticed that a research from Grinspon et al (23), they recommended basal LH 0.1 IU/L and LH/FSH 0.29 in CHH patients, which were in line with ours this study on base LH level, LH 0.16 ± 0.10 IU/L and 0.37 ± 0.27. In Grinspon's study, there was no specific time points for children with pump treatment, whereas we performed LHRH stimulation tests in patients receiving pump therapy to determine the cut-off values of hormone levels at specific

follow-up time points. Thus, this prospective study was able to determine more relevant LH ranges to determine the initiation and maturation of the HPG axis.

INH-B is the primary active inhibin in males (24–26). To date, a few studies have been conducted to investigate the effects of INH-B on puberty and development in males. INH-B produced by Sertoli cells was able to establish feedback, indicating developmental maturation(11;12). This study showed that INH-B and FSH concordantly rose firstly and were more sensitive than AMH. The cut-off value of INH-B was 54.5 pg/mL initiation of puberty. At the end of week12 of pump therapy, INH-B continued to rise, then T level increased, and FSH stabilized. At this point, the cut-off value of INH-B was 79.6 pg/mL, which was close to the normal reference value for adults (> 80 pg/mL)(27). Thus, INH-B 54.5–79.6 pg/mL indicated a consistent developmental stage of puberty. INH-B could present the first signal of puberty and maturation of Sertoli cells. In addition, AMH levels maintain high from infancy to adulthood, suggesting that AMH was the real inhibitor of the HPG axis, consistent with the findings of previous studies that showed that AMH peaked before puberty (G1), began to decrease during G2, and remained at low levels during G3 and thereafter (maturation stage) (19).

2. Hormonal changes and cut-off values after LHRH stimulation tests at different developmental stages

Hormone basal levels are highly specific indicators for clinical manifestations but are less sensitive than stimulation tests for early detection of puberty. The cut-off value of stimulated LH was 4.45 IU/L and LH/FSH was 0.54. they are almost the same as the current girl reference values LH 3–5 IU/L and LH/FSH 0.6 (6), providing further support for our hypothesis: no significant difference in hormone levels for initiation of puberty between boys and girls, so as the findings by Grinspon et al (23) (LH 1.4 IU/L and LH/FSH 0.63 after stimulation in CHH patients). Furthermore, this study was more rigorous and reliable. Thus, we recommend stimulated LH > 4.45 IU/L and LH/FSH > 0.54 as the indicators of initiation of puberty.

3. Pituitary response

GnRH pump therapy is safe and effective(13); but it is important to determine whether pump therapy is indicated for patients with pituitary disorders. GnRH pulse therapy (draft) (28) is not an indicator for pituitary disorders. Wu et al (20) retrospectively analysed the effects of GnRH pump therapy in patients with congenital combined pituitary hormone deficiency (CCPHD) and found that LH < 2 IU/L after 1 month of treatment was associated with no increase in T levels, suggesting that pump therapy was contraindicated if LH < 2 IU/L, as it indicated a poor pituitary response. In our study, all of the patients reached puberty after pump therapy, indicating that all of the patients had normal pituitary responses and were indicated for pump therapy. At the same time, we found that the excitation level of LH was 2.85 IU/L before treatment and one week after treatment, and the basal LH was 2.96 IU/L at 4 weeks after treatment. These three data were almost at the same level. So, we analysed hormone levels in these patients. The median of stimulated LH is 2.41 IU/L. The 95% confidence interval is (1.81–3.17) IU/L. Combined with the adult study (LH < 2 IU/L), it was considered that the level of LH was about 2 IU/L,

showed normal pituitary responses. Concurrently, we also analysed LH/FSH. The results showed that the median LH/FSH was 0.65 and 95% confidence interval (0.57–0.87) after stimulation.

In short, this is a prospective study with a novel design and reliable results with clinical value. The pre-puberty normal boys' basal LH level was 0.16 ± 0.10 IU/L. FSH, 0.65 ± 0.58 IU/L. During puberty: FSH is increased firstly, followed by INH-B and then LH and T. Finally, AMH decreased. And the decrease in stimulated LH/FSH and the increase in INH-B preceded puberty. The cut-off LH values at initiation of puberty and developmental maturation in boys, which were similar to the reference values in girls. Once the HPG axis was activated, there are no significant differences in hormones after stimulation. LH in the range of 1.81–3.17 IU/L and the LH / FSH in the range of 0.57–0.87 indicated that the pituitary response of CHH is well, and clinicians can use GnRH pump to treat them. To further improve the reliability of diagnosis and scientific rigor, future research may validate the results with additional patients and the time points identified in this study.

This study has some limitations: we only investigated classical hormones such as LH, FSH, T, AMH, and INH-B. we didn't study some recently new biomarkers such as insulin-like growth factor-3 and Kisspeptin, they were raised as related to the initiation of puberty and developmental maturation in boys with interactions with LH and FSH (29–32).

Conclusions subheading
We got the changes of puberty hormones in CHH boys. In clinic, we can use these hormones to further judge the adolescent development of boys.

Abbreviations

CHH
congenital hypogonadotropic hypogonadism
ROC
Receiver operating characteristic
LH
luteinizing hormone
FSH
follicle-stimulating hormone
T
Testosterone
AMH
anti-Mullerian hormone
INH-B
inhibin B
KS
Kallmann's syndrome

AUC
area under the curve

Declarations

Acknowledgments:

The authors have no acknowledgements.

Author's contributions

Chunxiu Gong performed clinical examination, diagnosis and treatment for this patient, also proposed views and revised the whole paper. Xiaoya Ren performed the collection and analysis of the clinical data and wrote the whole paper. YuanyuanTian, Guoshuang Feng, Yi Wang, Beibei Zhang, Bingyan Cao and Jiajia Chen contributed clinical thought to the part of discussion.

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Availability of data and materials

Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information.

Ethics approval and consent to participate

The research protocol was approved by the ethics committee of Beijing Children's Hospital, Capital Medical University (ID2012-28), and written informed consent was received from all patients or legal guardians.

Consent for publication

Consent was obtained from all patients for publication

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

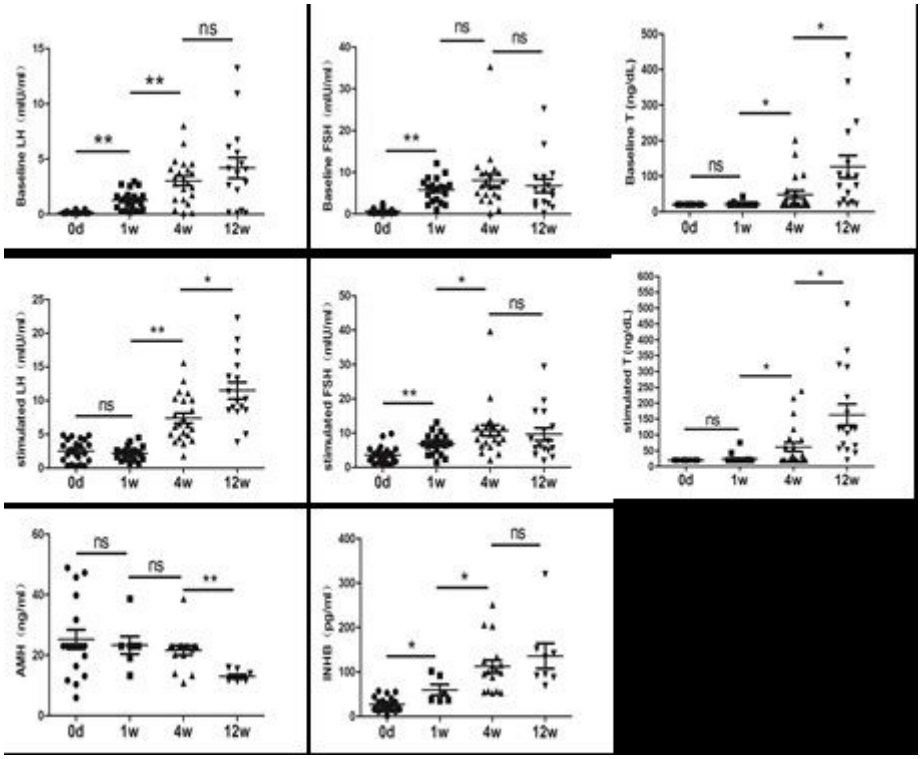

Figure 1

Hormone changes in CHH

Supplementary Files

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