Original research article

A retrospective study to assess penial development in response to hormone therapy in children diagnosed with micropenis

Dr. Md. Hedayatullah¹, Dr. C.M. Narain²

¹Senior Resident, Department of General Surgery, Government Medical College, and Hospital, Bettiah, Bihar, India
²Associate Professor, Department of General Surgery, Government Medical College, and Hospital, Bettiah, Bihar, India

Corresponding Author: Dr. C.M. Narain

Abstract

Aim: To evaluate the penial growth in response to hormone treatment in children with micropenis.

Methods: This retrospective study which was carried in the Department of General surgery, Government medical College, and Hospital Bettiah, Bihar, India for 1 year. 50 children (<18 years) who met the criteria for micropenis were included in this study. Children more than 10 years old (pubertal/post pubertal) were treated using a standard protocol of 1,500 to 2,000 IU hCG administrated intramuscularly, once per week, for 6 weeks, whereas children less than 10 years old (prepubertal) were treated with parenteral testosterone enanthate 25 mg once a month for 3 months. Measurement was made along the dorsum of the penis to the tip of the glans penis.

Results: Total 50 children presented with micropenis. Their mean age was 10.06 ± 4.07 years (range: 3-15 years). In children less than 10 years of age, mean penile length increased significantly after hormonal treatment from 16.08 mm to 36.73 mm (Table 2). In children greater than 10 years, serum testosterone level increased significantly after 8 weeks of hormonal treatment from <20.5 to 457.44 ±7.23 ng/ml (P < 0.0001). The mean penile length also increased significantly from 26.53 mm to 65.39 mm (P < 0.001). In the older children, mean testicular volume increased from 8.01 cc to 9.70 cc on the left side and from 5.42 cc to 6.97 cc on the right side (P < 0.005) after hormonal treatment. There were no significant adverse events related to the hormonal treatment.

Conclusion: Exogenous administration of testosterone to pre-pubertal boys and hCG to pubertal or post-pubertal boys results in significant increase in stretched penile length. This may be the primary form of treatment for micropenis in these children.

Keywords: micropenis, hormonal treatment, testosterone

Introduction

Micropenis the term refers to a specific disorder that has a specific set of causative factors and a different set of treatment modalities than the broader term of inconspicuous penis or, apparently, small penis, in lieu of which it is generally used. It would therefore behove us to understand fully the meaning and genesis of micropenis to better differentiate it from the other types of inconspicuous penis. The definition of micropenis hinges on the idea of stretched penile length, or SPL. SPL was first introduced by Schonfeld and Beebe¹ in their seminal work determining standard penile length according to age. Micropenis is defined as a SPL 2.5 standard deviations less than the mean for age group² without the presence of any other penile anomalies, such as hypospadias. Thus, for newborn term infants, a SPL of 1.9 cm or less is micropenis. As with many genital disorders, an understanding of the relevant embryology allows a better understanding of the condition itself. Beginning at 8 weeks of...
gestation, maternal chorionic gonadotropins from the placenta begin to stimulate testosterone production from the fetal Leydig cells. Under the influence of dihydro testosterone, a conversion product of testosterone, penile differentiation occurs. The genital tubercle differentiates into the glans penis, the genital folds become the shaft of the penis, and the genital swellings migrate to the midline to become the scrotum. Penile differentiation is complete by 12 weeks of gestation. During the second and third trimester, growth of the penis is accomplished through fetal androgens, which are produced under stimulation by fetal pituitary gonadotropin. There is a marked increase in penile size over that time period, with the penis growing almost 20 mm from weeks 16 to 38. Therefore, true micropenis must result from a hormonal abnormality that occurs after 12 weeks of gestation. Studies of genital skin fibroblasts in patients with micropenis have shown normal androgen production and action after administration of gonadotropins, as well as appropriate receptor activity, which reinforces the central role the hypothalamic-pituitary axis played in the genesis of micropenis. True micropenis is a result of a hormonal abnormality occurring after 12 weeks of gestation. The causes of this condition can be divided into three broad groups: hypogonadotropic hypogonadism (pituitary/hypothalamic failure), hypergonadotropic hypogonadism (primary testicular failure), and idiopathic. These represent the most common etiologies of micropenis.

Once micropenis is confirmed through physical exam, consultation with the endocrinology service should be obtained to help determine the cause of micropenis as well as to rule out possible lifethreatening associated abnormalities. Specifically, hypogonadotropic hypogonadism is commonly associated with growth hormone (GH) deficiency and/or adrenocorticotropic hormone (ACTH) deficiency, putting the infant at high risk for death due to hypoglycemia or cortisol deficiency. Plasma cortisol, serum electrolytes, and plasma glucose may be obtained in this setting to rule out acute problems. The endocrinologic evaluation can also isolate the cause of micropenis to its level in the hypothalamic-pituitary-testicular axis. Specifically, prolactin (PRL) levels help to isolate the defect to the hypothalamus (high PRL) vs. the pituitary (low PRL). In addition, plasma GH, thyroid stimulating hormone (TSH), and ACTH can all be used to isolate the location of dysfunction. Interestingly, it may be difficult to make the diagnosis of hypogonadotropic hypogonadism in the prepubertal patient with micropenis if they are past infancy, as there is a quiescent phase of the pituitary that sees levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) drop precipitously.

Material and methods
This retrospective study which was carried in the Department of General Surgery, Government medical College, and Hospital, Bettiah, Bihar, India for 1 year. after taking the approval of the protocol review committee and institutional ethics committee.

Inclusion criteria
Children (<18 years) who met the criteria for micropenis were included in this study.

Exclusion criteria
Children with cryptorchidism or absence of testis according to the imaging studies conducted at the initial presentation were excluded from the study. Similarly, children with hypospadias were also excluded from the study.

Methodology
The hCG stimulation test was not performed in any of the children. Pretreatment estimation of serum LH, follicle-stimulating hormone (FSH) and testosterone was done in all
(pubertal/postpubertal) children more than 10 years old. A diagnosis of IHH was made on the basis of low or normal serum LH and FSH concentrations associated with low serum testosterone. Testis volume was assessed in children more than 10 years old using the Prader orchid meter. Penis length (flaccid and stretched) and testicular volume were measured before and after hormonal treatment in all children. Children more than 10 years old (pubertal/postpubertal) were treated using a standard protocol of 1,500 to 2,000 IU hCG administrated intramuscularly, once per week, for 6 weeks, whereas children less than 10 years old (prepubertal) were treated with parenteral testosterone enanthate 25 mg once a month for 3 months. This change in treatment plan depending on age was followed so as to promote the older child’s own testes to produce testosterone. Penile length was measured by the same physician. A wooden spatula was pressed against the pubic ramus depressing the suprapubic pad of fat as completely as possible to ensure that the part of the penis that is buried in the subcutaneous fat was measured. Measurement was made along the dorsum of the penis to the tip of the glans penis. The length of foreskin was not included.

Statistical analysis

The data are given as the mean ± SD unless otherwise indicated. Comparisons of data within a patient were evaluated by Student’s t-test; comparisons of data from different subsets were evaluated by unpaired t-test.

Results

Total 50 children presented with micropenis. The clinical features of the children are shown in Table 1. Their mean age was 10.06 ± 4.07 years (range: 3-15 years).

In children less than 10 years of age, mean penile length increased significantly after hormonal treatment from 16.08 mm to 36.73 mm (Table 2). In children greater than 10 years, serum testosterone level increased significantly after 8 weeks of hormonal treatment from <20.5 to 457.44 ±7.23 ng/ml (P < 0.0001). The mean penile length also increased significantly from 26.53 mm to 65.39 mm (P < 0.001) [Table 2]. In the older children, mean testicular volume increased from 8.01 cc to 9.70 cc on the left side and from 5.42 cc to 6.97 cc on the right side (P < 0.005) after hormonal treatment [Table 3]. There were no significant adverse events related to the hormonal treatment.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Children (&lt;10 years)</th>
<th>Children (&gt;10 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of children</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>6.78±1.73</td>
<td>13.2±1.21</td>
</tr>
<tr>
<td>Penile length (mm)</td>
<td>16.08±2.91</td>
<td>27.02±10.27</td>
</tr>
<tr>
<td>Hormonal assay Serum LH (mIU/mL)</td>
<td>—</td>
<td>0.53±0.041</td>
</tr>
<tr>
<td>Serum FSH (mIU/mL)</td>
<td>—</td>
<td>0.251±0.137</td>
</tr>
<tr>
<td>Serum testosterone (ng/dL)</td>
<td>—</td>
<td>&lt;20.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>After 8 weeks</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum testosterone ng/ mL (Children &gt;10 years old)</td>
<td>&lt;20.5</td>
<td>457.44 ±7.23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum testosterone ng/ mL (Children &lt;10 years old)</td>
<td>—</td>
<td>387.38 ±8.69</td>
<td></td>
</tr>
<tr>
<td>Penile length mm (Children &gt;10 years old)</td>
<td>26.53 ±9.889</td>
<td>65.39±4.37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Penile length mm (Children &lt;10 years old)</td>
<td>16.11±2.96</td>
<td>38.03±2.57</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Table 3: Testicular volumes before and after hormonal treatment

<table>
<thead>
<tr>
<th>Testicular volume mL</th>
<th>Baseline</th>
<th>After 8 weeks</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>8.01±1.67</td>
<td>9.70±2.09</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Right</td>
<td>5.42</td>
<td>6.97</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Discussion

Micropenis refers to an extremely small penis with a stretched penile length of less than 2.5 SD below the mean for age or stage of sexual development.\(^{11-14}\) The ratio of the length of the penile shaft to its circumference is usually normal, but occasionally, the corpora cavernosa are severely hypoplastic. The testes are usually small and frequently crypt orchid, whereas the scrotum is usually fused. Stretched penile length is used as a measure because it correlates more closely with erectile length than does relaxed penile length. Measurements should be compared with existing standards for penile length. Micropenis needs to be differentiated from a webbed or buried penis. The initial evaluation of a child with micropenis should include a thorough medical history and a karyotype at birth. Accurate measurement of the penile length, palpation of the corporeal bodies, and evaluation for cryptorchidism are several important aspects of the physical examination. Kumanov et al.\(^{15}\) prospectively studied Bulgarian boys and established wide regional variation of normal penile lengths. It is very important to consider regional as well as ethnic differences while approaching diagnostic and therapeutic considerations. Consultation with a pediatric endocrinologist is also usually obtained to determine the cause of micropenis and to assess whether other abnormalities are present. Several issues need to be addressed, including the growth potential of the penis and the etiology of the micropenis. Testicular function may be assessed by measuring serum testosterone levels before and after hCG stimulation. Primary testicular failure produces an absent response and elevated basal concentrations of LH and FSH. Endocrinologic evaluation can also isolate the cause of micropenis to its level in the hypothalamic-pituitary-testicular axis. Specifically, prolactin (PRL) levels help isolate the defect to the hypothalamus (high PRL) versus the pituitary (low PRL).\(^{16}\) In addition, plasma GH, thyroid stimulating hormone, and adrenocorticotropic hormone (ACTH) can all be used to isolate the dysfunction. Interestingly, it may be difficult to make the diagnosis of hypogonadotrophic hypogonadism in the prepubertal patient with micropenis if they are past infancy, as there is a quiescent phase of the pituitary that sees levels of FSH and LH drop precipitously.\(^{16}\) Sometimes, extensive evaluation of the hypothalamic-pituitary-testicular axis needs to be done before androgen therapy is administered to determine the end organ response. Several studies have shown that patients with IHH had a good response to hCG therapy in terms of penile growth, testicular growth, and elevation of serum testosterone.\(^{17}\) Treatment of micropenis should focus on penile size sufficient for the child to have an appropriate body image, normal sexual function, and standing micturition. Inability to bring the penis fully to the mean measurement for age does not imply failure. Primary treatment of micropenis revolves around exogenous testosterone administration to increase the length of the penis so that it may be considered within a range of normal. Good responses are typically seen with increases of over 100% in penile length over the course of initial treatment to be expected.\(^{18-20}\) Kim et al.\(^{17}\) included 20 IHH patients who met the criteria for micropenis and were administrated hCG intramuscularly, 3 times per week, for 8 weeks. The mean serum testosterone level was significantly increased after hCG treatment (P < 0.05). In children less than 10 years of age, mean penile length increased significantly after hormonal treatment from 16.08 mm to 36.73 mm. In children greater than 10 years, serum testosterone level increased significantly after 8 weeks of hormonal treatment from <20.5 to 457.44 ±7.23 ng/ml (P < 0.0001). The mean penile length also increased significantly from 26.53 mm to 65.39 mm (P < 0.001). In the
older children, mean testicular volume increased from 8.01 cc to 9.70 cc on the left side and from 5.42 cc to 6.97 cc on the right side (P < 0.005) after hormonal treatment. Schiphol et al. reported that gonadotropin therapy with 3 × 2,500 IU hCG as a weekly intramuscular injection restored endocrine and exocrine testicular function to the normal range in male patients with IHH. They showed that the serum level of testosterone, positive sperm count, and testicular volume was increased significantly in the gonadotropin-injected group. Apart from primary treatment of micropenis, repeat hormone administrations may be performed over short-time periods if the response is not deemed satisfactory. There have been concerns about the administration of testosterone to prepubertal patients and the impact on their ultimate penile length. Current long-term data regarding patients treated in childhood with exogenous testosterone have shown no reduction in adult penile length.

**Conclusion**

Exogenous administration of testosterone to pre-pubertal boys and hCG to pubertal or post-pubertal boys results in significant increase in stretched penile length. This may be the primary form of treatment for micropenis in these children.

**Reference**


Received: 11-10-2020  Revised: 18-11-2020  Accepted: 20-11-2020