



## Essential Pathogenesis Diagnosis Provides Best Treatment Option for Hypospadias

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### Abstract

Hypospadias is one of the most common congenital malformations occurring in male fetuses. For surgeons, hypospadias is only a clinical manifestation and mostly diagnosed just by its clinical manifestation. Before surgery, all patients received a detailed clinical evaluation including measurement of type of hypospadias, the size of the penis, glans cleft, and type of chordee, penile torsion, urethral plate width, prepuce and associated anomalies. Each patient received a clinical diagnosis for hypospadias. Hypospadias repairs were performed on 53 patients aged 2 to 32 years from 2010 to 2014, including 47 primary operations and 6 reoperations. Hypospadias is mostly a clinical manifestation for surgeons. In the management of hypospadias preoperative assessment is of prime importance, but the assessment usually includes factors only related to the operation such as location and size of the meatus, the size of the phallus, urethral plate width, and type of chordee. It is no doubt that all these factors would affect the outcome of surgery.

**Keywords:** Hypospadias; Disorders of sexual development; 5 $\alpha$ -reductase-2 deficiency

### Introduction

Hypospadias is one of the most common congenital malformations occurring in male fetuses. For surgeons, hypospadias is only a clinical manifestation and mostly diagnosed just by its clinical manifestation.

In fact interactions between genetic and environmental factors may contribute to its pathogenesis [1]. The heritability is the highest identified risk factor for hypospadias so lots of candidate genes and polymorphisms have been suggested. On the other hand, 46 XY Disorders of Sexual Development (DSD) or other genetic related syndromes such as Partial Androgen Insensitivity Syndrome (PAIS), 5 $\alpha$ -reductase-2 deficiency would also result in the clinical manifestation of hypospadias [2,3].

Hypospadias urethroplasty is a challenging field of urogenital reconstructive surgery with different techniques and it is considered difficult as the complications and unfavorable results are not uncommon. The complication rate after hypospadias repairs ranges from 5% to 70% [4]. For patients with hypospadias, many surgeons only focused on the types or severity of the diseases, however the exact pathogenesis diagnosis was usually neglected and the choice of which surgical procedures depends more on surgeon's experience, therefore the outcome also differed among patients. It was reported that the reoperation rates after primary procedures can exceed 50% [5]. The reoperation rates may partly related to surgical skills or clinical experience, however, surgical repair alone without correct pathogenesis diagnosis would also cause unsatisfactory outcome. Hypospadias repair surgery may improve in urination and appearance, but the prospective functional development usually requires further treatment based on specific pathogenesis diagnosis.

In our study, we aim to summarize our efforts for seeking pathogenesis diagnosis for hypospadias and contributing to the best treatment option for these patients.

### Methods

This was a prospective study including 53 patients under hypospadias repairs in Shanghai Ninth People's Hospital between January 2010 and June 2014. Before surgery, all patients received a detailed clinical evaluation including measurement of type of hypospadias, the size of the penis, glans cleft, and type of chordee, penile torsion, urethral plate width, prepuce and associated anomalies. Each patient received a clinical diagnosis for hypospadias.

Transverse Island Flap (TVIF) onlay technique was used for hypospadias repair. A total of 53 patients with hypospadias repair were included in the study and six patients among them were

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performed secondary surgery because of complications after first surgery performed in other hospital. The average follow-up for patients after surgery was 12.5 months. For reoperation patients in our study, blood samples were collected for serum hormone tests and gene analysis. All patients with secondary surgery were followed up till one year and further exams were performed for a more precise pathogenesis diagnosis.

## Results

Hypospadias repairs were performed on 53 patients aged 2 to 32 years from 2010 to 2014, including 47 primary operations and 6 reoperations. All patients received a clinical diagnosis, among all patients mid-penile hypospadias (distal penile, mid shaft, and proximal penile) was the most common type among them accounting for 47.2% (n=25) patients. Penoscrotal hypospadias accounting for 24.5% (n=13) and subcoronal for 28.3% (n=15) patients. In our series, chordee was seen in 23 (43.4%) patients. On follow-up the chordee was corrected and cosmetic appearance of the penis was excellent in 94.3% (n=50) the patients. There were two patients have urinary fistula after primary hypospadias repairs and asked for fistula repair. The complication rate was 3.8%.

Three patients were diagnosed as PAIS and five patients as 5 $\alpha$ -reductase-2 deficiency after surgery by gene screening. So the pathogenesis diagnosis rate was 15.1% (n=8) in our study. For two patients with PAIS, one had been diagnosed early and treated with effective hypospadias repair and supporting treatment; however, the other patient had hypospadias operation before pathogenesis diagnosis in local hospital, which resulted in unsatisfactory outcome with undeveloped micropenis and chordee. Therefore he decided to have micropenis removal and penis reconstruction surgery in our hospital.

### Case 1

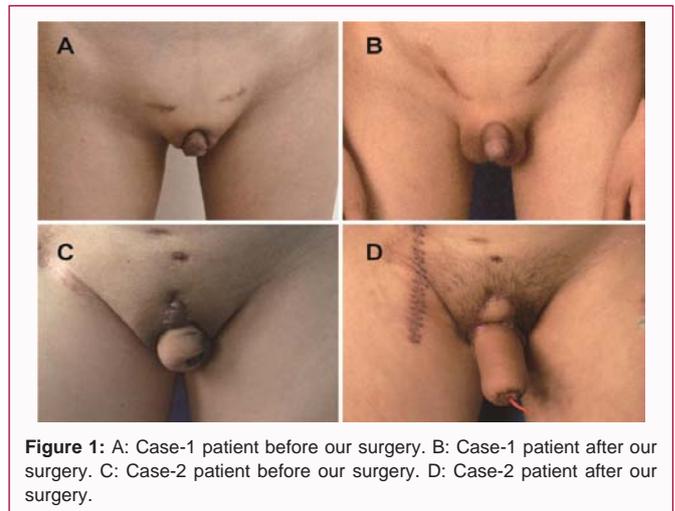
A 13-year-old child had penoscrotal hypospadias, micropenis and cryptorchid since born. He was tested for serum hormone level and testicular biopsy two years ago and diagnosed for PAIS in other hospital. After than he take testosterone treatment for 8 weeks. He came to our hospital and asked for hypospadias repair in 2013. Combined treatment with hormone supporting treatment, he had a satisfactory outcome after surgery.

### Case 2

A 38-year-old man was diagnosed as hypospadias since born. He had hypospadias repair 15 years ago and penis lengthening surgery 2 years ago in other hospital but the chordee and micropenis disorder still existed with age. For a pathogenesis diagnosis, the serum hormone level was tested showed elevator T and E2, and gene analysis indicated AR mutation. Finally he was diagnosed for PAIS. After that he came to us for micropenis removal and penis reconstruction surgery (Figure 1).

## Discussion

Hypospadias is mostly a clinical manifestation for surgeons. In the management of hypospadias preoperative assessment is of prime importance, but the assessment usually includes factors only related to the operation such as location and size of the meatus, the size of the phallus, urethral plate width, and type of chordee. It is no doubt that all these factors would affect the outcome of surgery. In most times, associated anomalies and hormone levels may not be regarded as the same importance. Therefore an exact pathogenesis diagnosis before



**Figure 1:** A: Case-1 patient before our surgery. B: Case-1 patient after our surgery. C: Case-2 patient before our surgery. D: Case-2 patient after our surgery.

surgery usually may not be obtained.

Although for most patients the pathogenesis diagnosis would not affect the treatment or prognosis if the surgery was well done, we cannot neglect the unfavorable consequence caused by a simple clinical diagnosis as hypospadias in some specific cases. We demonstrated two hypospadias cases whose outcome highly related to the time they got the pathogenesis diagnosis, which implied importance of the intervention based on pathogenesis besides surgery. The case-1 patient received a specific diagnosis as PAIS before surgery and treated with testosterone supporting treatment, which made it easier to obtain a good outcome and prognosis after operation. On the other hand, the case-2 patient got pathogenesis diagnosis after hypospadias repair so that other associated anomalies did not be corrected with surgery. Although we had successfully reconstructed the penis with operation, he might have a better outcome if the pathogenesis diagnosis was made in time.

Hypospadias is now regarded as a typical clinical manifestation for undervirilized 46 XYDSD. Meanwhile hypospadias is also one classic feature of many syndromes including PAIS and 5 $\alpha$ -reductase-2 deficiency. It had reached agreement that best options of treatment for Complete Androgen Insensitivity Syndrome was gonadectomy and vaginal surgery, but for PAIS patients, it was hard to find a best option since difficulty in reaching a decision on sex assignment and early management issue [3]. Moreover, patients with PAIS did not differ from the vast majority of hypospadiac patients [6]. However, if acute pathogenesis diagnosis could be made early before treatment decision, it may provide a better option. For 5 $\alpha$ -reductase-2 deficiency patients, most of them are reared in the female social sex due to their severely undervirilized external genitalia [7]. Traditionally, the diagnosis relies on Dihydrotestosterone (DHT) measurement, but the results are often equivocal, potentially leading to misdiagnosis [8]. Therefore, a confirmed diagnosis required genetic analysis [8,9]. For those patients, a simple hypospadias repair would not correct the whole picture, and best treatment options are still based on the pathogenesis diagnosis. Retrospecting our clinical work, we suggested a pathogenesis diagnosis before a simple hypospadias repair may provide best outcome for DSD patients.

Hormone therapy preceding hypospadias correction is still a controversial subject, and there is no consensus about the dose and time of application of hormone therapy [10]. So it is not appropriate for each hypospadiac patient receiving hormone therapy prior to

surgery. For each idiopathic hypospadias patient with any associated anomalies such as cryptorchidism or other may relate to DSD, we suggested an essential pathogenesis diagnosis before surgery. Since the sex development is represented by the genes, gonads, hormonal machinery and tissue targets of the patients [11], serum hormone level would be an easy mark to distinguish those patients with simple hypospadias if gene screening is not available. For urology and plastic surgeons, pathogenesis diagnosis would cause less complications and secondary surgeries and provide best treatment option for patients.

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