

MALE PSEUDOHERMAPHRODITISM: ETIOLOGICAL EVALUATION, SURGICAL TREATMENT, AND THE INCIDENCE IN RELATION TO INGUINAL HERNIA

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Male pseudohermaphroditism (MPH) is defined broadly as incomplete masculinization of the external genitalia in a male (46XY) karyotype.¹ There are several causes of MPH. According to Sinnecker's classification of MPH, there is a spectrum of the phenotype of the external genitalia in these patients, where on one side of the spectrum, there is the completely phenotypic female, on the other side, the anatomically normal male with impaired spermatogenesis and/or pubertal virilization, and in between, an area of ambiguity.² Each of these cases poses both a diagnostic and therapeutic challenge to the treating physician. The diagnosis in those with normal-appearing female external genitalia may be made during infancy and childhood when they present with inguinal hernias that are found to contain testes, but more commonly, the diagnosis is delayed until late adolescence during the investigation of primary amenorrhea.^{1,3,4} In this report, we present two cases of male pseudohermaphroditism who presented with inguinal hernias, outlining aspects of diagnosis and treatment. The incidence of MPH in relation to inguinal hernia is also reported.

Patients and Methods

Over a period of 10 years from 1989 to 1998, a total of 970 children had inguinal hernia repair at our hospital. There were 827 males and 143 females (M:F 5.8:1). Females formed about 14.6% of the total number of children with inguinal hernias. Of the 143 females, 32 presented with bilateral inguinal hernias (16 had metachronous bilateral hernias and 16 had synchronous bilateral hernias). During the same period, only two of those who presented with bilateral inguinal hernias were found to have MPH. Thus, in our study, MPH presenting as an inguinal hernia represented about 1.4% of all female children presenting with inguinal hernias, 6.3% of female children presenting with bilateral hernias and 12.5% presenting with bilateral synchronous inguinal hernias.

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Case Reports

Case 1

A two-week-old infant was referred to our clinic with bilateral inguinal hernia. She was a product of full-term normal vaginal delivery, with a birth weight of 2.5 kg. Clinically, she was a phenotypically normal female with bilateral inguinal hernias. No palpable masses were detected. The parents were advised that she have surgery but wanted to wait. She presented again at the age of three years with the same complaint and clinically no abnormality could be detected apart from the bilateral inguinal hernias. She underwent bilateral inguinal herniotomies and during surgery, the hernial sacs were found to contain testes on both sides (Figure 1). The herniotomies as well as testicular biopsies were performed.

Postoperatively, the patient's investigations revealed: Na⁺ 137 mEq/dL, K⁺ 4.2 mEq/dL, Ca 9.5 mg/dL, phosphorous 4.1 mg/dL, Hb 9.6 g/dL, WBC 9.0x10²/mm³, and platelets 296,000/mm³. Her abdominal and pelvic ultrasound showed no evidence of a uterus. Chromosomal analysis showed 46XY chromosomes. Her follicle-stimulating hormone (FSH), cortisol, luteinizing hormone (LH) and DHEAS levels were normal. Her basal testosterone level was 2.2 nmol/L (normal range, 0.2-

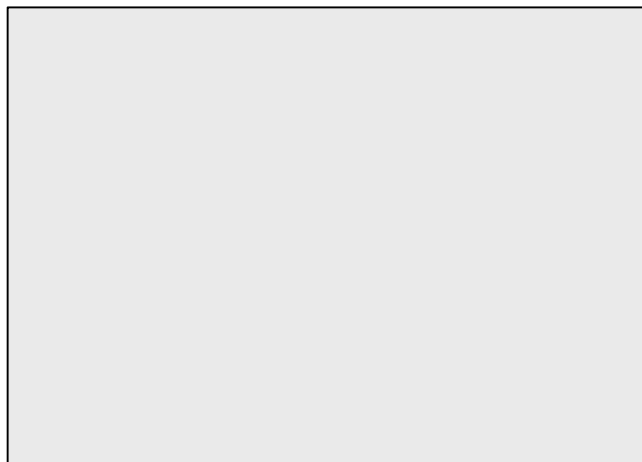


FIGURE 1. Intraoperative photograph showing bilateral testes in a phenotypic female with inguinal hernia.

3.4 nmol/L). Microscopic examination of both specimens revealed testicular tissue. A thorough consultation with the parents was done and the condition explained to them, as well as the need for bilateral orchidectomy. About five weeks later, the patient was subjected to bilateral orchidectomy and during surgery, examination under anesthesia revealed normal-looking female external genitalia as well as a vagina. Postoperatively, the patient recovered well and she is being followed up in the pediatric endocrinology clinic. She will need hormone replacement therapy at the time of her menarche and this was stressed to the family.

Case 2

This patient presented to our hospital at the age of 6 years as a case of congenital adrenal hyperplasia. She was being followed up in another hospital from birth as a case of recurrent attacks of vomiting and dehydration. At the age of five months, she was diagnosed with congenital adrenal hyperplasia, when her Na^+ was found to be 122 mmol/L, and with increased urinary Na^+ , and so she was started on treatment. Two of her sisters died at 4 and 6 months of age, and a third sister is receiving hormonal treatment and being followed up in another hospital. At the age of 3½ years, she had right inguinal herniotomy in another hospital, during which a gonad resembling a testis was found in the hernial sac. This was not excised or biopsied.

At the time of referral to our hospital, the patient was phenotypically female, with normal-looking external genitalia. She was also found to have recurrent right and left inguinal hernias. Both hernias had a palpable gonad. Her investigation revealed Na^+ 134 mmol/L, K^+ 3.2 mmol/L, free testosterone 0.18 pg/mL, 17-hydroxy progesterone <0.1 mg/mL, DHEAS <0.5 µg/dL, and ACTH 619 pg/mL (normal range 10.6-68.6). Her testosterone level did not rise following B-hCG stimulation test. Abdominal and pelvic ultrasound showed no uterus, but both inguinal regions showed oval structures suggestive of undescended testes. Her chromosomal analysis revealed 46XY genotype. She was diagnosed as 20,22-desmolase deficiency. She underwent lower abdominal laparotomy which revealed no uterus or ovaries. Two abdominal testes were found and were confirmed by frozen section. Bilateral orchidectomies as well as bilateral inguinal herniotomies were done. Postoperatively, the patient recovered well, and was discharged in a good condition. She is on treatment for her associated congenital adrenal hyperplasia and the need for hormone replacement therapy at her menarche was also stressed to the family.

Discussion

A variety of clinical conditions can lead to the appearance of ambiguous genitalia in a newborn infant. Although there are several classifications of intersex disorders, the four major pathological groups are: female

pseudohermaphroditism, mixed gonadal dysgenesis, male pseudohermaphroditism, and true hermaphroditism. Among these, congenital adrenal hyperplasia is the most common cause of ambiguous genitalia.⁵

Male pseudohermaphroditism is defined as incomplete masculinization of the external genitalia in patients with normal karyotype (46XY). The appearance of the external genitalia in these patients depends on the cause, and ranges from mild hypospadias with some clitoral hypertrophy to complete phenotypic females.³ Male pseudohermaphroditism can be caused by one of many defects.⁶ The first are defects in testosterone synthesis, which are attributed to five enzymatic defects along the synthetic pathway of testosterone from cholesterol. Enzymatic defects in testosterone biosynthesis are very rare. A review of a large series of 25 children with male pseudohermaphroditism by Berkovitz et al. showed that none of the cases were due to enzymatic defects in testosterone biosynthesis.⁷ Similar findings were shown by Coran and Polley,⁵ and Taha and Magbool.⁸ Patients with the more proximal enzymatic blocks in the cholesterol to testosterone pathway (20,22-desmolase, 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase deficiencies) resemble congenital adrenal hyperplasia as well as male pseudohermaphroditism in their presentation.⁶ These patients usually present early with severe salt wasting, and if not recognized and treated early, the condition may lead to death.

Our second patient presented early with features of congenital adrenal hyperplasia, but was not diagnosed accurately until the age of six years. Distal enzymatic defects in the pathway (17,20-desmolase, 17β-hydroxysteroid dehydrogenase deficiencies), on the other hand, result in incomplete masculinization only.⁶ The second cause of male pseudohermaphroditism is androgen receptor disorder. This is also called androgen insensitivity syndrome and is divided into two phenotypic forms: the complete form and the partial form.⁴ In the complete form, previously known as the testicular feminization syndrome, the patient has normal female external genitalia. Our first patient had complete androgen insensitivity syndrome, and apart from bilateral inguinal hernias that contained testes, there were no other abnormalities.

Although these patients may present early with inguinal hernia, they are more commonly discovered late during the evaluation of amenorrhea. Patients with the partial form of androgen insensitivity syndrome, on the other hand, present early with ambiguous genitalia, usually in the form of clitoromegaly with severe hypospadias. In both conditions, there is absence of female internal reproductive organs, which can be verified by ultrasound or laparoscopy, and since androgen insensitivity syndrome occurs because of some abnormality in the androgen receptor, the plasma testosterone levels are within normal and when subjected to human chorionic gonadotropin stimulation test, there is a normal response, which shows that Leydig cells are

functionally normal. The androgen insensitivity syndrome results from a mutation of the androgen receptor gene. Androgen binding can be evaluated in fibroblasts derived from genital skin biopsies as well as DNA analysis.⁹ Recently, the sex hormone-binding globulin test has been shown to provide functional information about the severity of the receptor defect.¹⁰ These tests are unfortunately not available at our hospital.

The third cause of male pseudohermaphroditism consists of defects in androgen action. These patients have a deficiency of 5 α -reductase enzyme and so are unable to convert testosterone to the more active dihydrotestosterone at the external genitalia target cells. These patients secrete normal testosterone and müllerian inhibitory factor, and so have normal internal male genitalia, and they present early with severe hypospadias. The activity of 5 α -reductase can be assessed by direct measurement of enzyme activity in cultured genital skin fibroblasts or by measurement of testosterone-dihydrotestosterone ratio and urinary androsterone-etiocholanolone ratio following human chorionic gonadotropin stimulation test.¹¹

In the evaluation of any child with ambiguous genitalia, it is essential to determine the karyotype. The presence of a male karyotype (46XY) in the presence of incomplete masculinization and bilateral testes establishes the diagnosis of male pseudohermaphroditism. Since some forms of male pseudohermaphroditism may present as salt-losing congenital adrenal hyperplasia, as in our second patient, it is essential to exclude this, since further evaluation and management of these cases vary from those with simple congenital adrenal hyperplasia. Although on rare occasions male pseudohermaphroditism may result from gonadal dysgenesis, these patients in addition have müllerian structures due to the lack of müllerian inhibitory factor. This can be determined via abdominal ultrasonography and genitography.

To assess the function of Leydig's cells in these patients we use the human gonadotropin stimulation test. In patients with gonadal dysgenesis, there is no or low testosterone level and no accumulation of testosterone precursors, while in patients with enzymatic defects, there is low testosterone level and accumulation of plasma precursors, depending on the site of block. This, however, is not the case where the defect is in 20,22-desmolase, the first step in the pathway from cholesterol to testosterone, where no rise in testosterone or testosterone precursors will be produced, as was the case in our second patient. These patients have bilateral testes, which differentiates them from cases of gonadal dysgenesis. In addition to this there is associated congenital adrenal hyperplasia from the lack of other corticosteroids and mineralocorticoids. The fact that 20,22-desmolase deficiency is familial, with an x-linked pattern of inheritance, calls for a thorough evaluation of other female members of the family. Two sisters of our second patient died early, most likely due to a similar problem, and the

third sister is receiving treatment in another hospital for a similar condition.

A fact that is of great importance in dealing with patients with ambiguous genitalia is early diagnosis and appropriate gender assignment. In the majority of patients with intersex disorders, the defects are apparent at birth. Although our two patients had intersex disorders, their external genitalia were phenotypically female. In spite of the male genotype, which was a total surprise to the parents, this female phenotype made a female gender the best choice for our patients.

Our two patients presented with bilateral inguinal hernias that contained testes. The exact incidence of male pseudohermaphroditism in females with inguinal hernias is not exactly known. Kaplan et al. estimated this incidence to be 1.4%.¹² This was our finding as well. The frequency rose to 6.3% in females with bilateral inguinal hernias and 12.5% in females with bilateral synchronous inguinal hernias. Although these are only rough estimations, they call for close attention during the evaluation of female children who present with inguinal hernia, especially those with bilateral synchronous inguinal hernias.

In the management of cases of male pseudohermaphroditism who are complete phenotypic females, such as our two patients, reconstructive surgery to the external genitalia is not required, but the gonads need to be removed because of the risk of malignancy.^{13,14} The timing of bilateral orchidectomy varies. There are those who prefer to delay orchidectomy until after puberty to avoid early estrogen replacement. Like others, we advocate early orchidectomy at the time of hernia repair,⁵ which in our setting is of great importance. This will obviate the psychological trauma to the patient and her parents if orchidectomy is delayed until puberty, and avoid the chance of the patient being lost during follow-up and so decrease the danger of malignant transformation. The importance of long-term hormone replacement therapy at the time of menarche must also be stressed to the parents.

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