Ambiguous Genitalia : An Overview of 22 Years Experience and the Diagnostic Approach in the Pediatric Department, Siriraj Hospital†

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Abstract

The newborn with abnormal genital development presents a difficult diagnostic and treatment challenge for the pediatrician providing care. It is important that a definitive diagnosis be determined as quickly as possible so that the appropriate treatment plan can be established to minimize medical, psychological and social complications. The purpose of this study was to provide an extensive review of the clinical characteristics of a patient cohort with ambiguous genitalia, from 22 years' experience in the Division of Endocrinology and Metabolism, Department of Pediatrics, Siriraj Hospital, and to classify them into diagnostic categories. Moreover, a cascade of diagnostic tools in approaching sexual ambiguity in the authors' institution, starting with history and physical examination and leading to further radiographic and laboratory investigations is demonstrated and can be adopted as a guideline for the clinical management of these disorders. From 1979 to 2001, care was provided to a total of 109 patients with ambiguous genitalia, of whom 104 patients were reviewed. Among these individuals, 52 patients (50.0%) belonged to the diagnosis of female pseudohermaphroditism, 5 patients (4.8%) were in the true hermaphroditism group and the remaining 47 patients (45.2%) were in the male pseudohermaphroditism group. All female pseudohermaphrodites carried a diagnosis of congenital adrenal hyperplasia (CAH) and were reared as girls. 21 hydroxylase deficiency CAH accounted for all except one (98%) in this group. Among the 47 male pseudohermaphrodites, 9 (19.1%) had dysgenetic male pseudohermaphroditism, 7 (14.9%) had either testosterone biosynthetic defects or hCG unresponsiveness, 22 (46.8%) had either androgen insensitivity syndrome or 5 α-reductase deficiency, 4 (8.5%) had ambiguous genitalia in a 46,XY male associated with multiple anomalies and 5 (10.6%) had an unidentifiable cause. Sex reassignment occurred, not uncommonly, in 4 cases of female pseudohermaphrodites (7.7%) and at least 2 cases

(3.9%) in the combined group of male pseudohermaphrodites and true hermaphrodites. The scope of the ambiguous genitalia problem is definitely not minor. An inappropriate approach to this problem poses an undue risk to the integrity of the physical and psychosexual health in the future for these children.

Key word : Ambiguity, Female Pseudohermaphroditism, Male Pseudohermaphroditism, True Hermaphroditism, Congenital Adrenal Hyperplasia, Gonadal Dysgenesis, Human Chorionic Gonadotrophin, Outcome Management, Müllerian Structure

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Genital ambiguity represents a heterogenous group of diagnoses and occurs once in every 4,500 births[1]. This condition can stem from either excessive intrauterine exposure of the female fetus to androgens (female pseudohermaphroditism), insufficient androgen stimulation of the male fetus (male pseudohermaphroditism), or chromosomal aberrations resulting in abnormal gonadal differentiation as seen in true hermaphroditism, mixed gonadal dysgenesis and some complex congenital syndromes [2]. In order for an infant to develop as a phenotypically complete male or female, a cascade of complex molecular and morphological events must take place at the appropriate time and in the correct sequence during ontogeny. Extensive review of the issue of human sexual differentiation is beyond the scope of this article but can be reviewed elsewhere[3-12].

The birth of a child with ambiguous genitalia constitutes a social emergency[7], a possible social and psychological tragedy can occur unless physicians formulate quickly a well-thought-out plan for action. It is not tenable to cloak the gender of the newborn in view of secrecy. Each infant requires individual consideration based on adequate information acquired from physical examination, laboratory studies and parental feelings. In many instances, transfer of the child to a tertiary care facility is the optimal plan. Undue delay can have far-reaching repercussions[13].

In Thailand, insight into the scope of the problems associated with these patients has been inadequate and therefore, many sensitive issues have been neglected or handled sophomorically. As a consequence, patients suffer physically and psychologically. Perhaps the lack of a systematic body of reporting and simplified guidelines for disclosing a diagnosis may contribute to the sub-optimal understanding of this condition within the medical community. Indeed, there have been only a handful of previous reports published regarding these disorders in Thais[14-16]. Hence, the authors collected data from a cohort of ambiguous genitalia patients from 1979 until 2001, an extensive experience of 22 years, and have presented them in this article. Patients were all diagnosed and followed-up at Siriraj Hospital. The aim of this study was to depict clinical phenotypes of sexual ambiguity and diagnosis categories, and to provide a line of diagnosis and management to urge healthcare professionals to become aware of this not so uncommon condition in the Thai population. It may also serve as basic data to initiate future research to extend the understanding of this heterogenous group of patients who

share similar clinical problems. In addition, a simplified framework for classifying sexually ambiguous patients utilized at our institution is proposed.

MATERIAL AND METHOD

The subjects were patients who presented with ambiguous genitalia from 1979 to 2001, at the Endocrine Division in the Department of Pediatrics, Siriraj Hospital. Data were collected retrospectively from review of the patient's notes.

Table 1 Diagnosis in ambiguous genitalia patients in this study.

Classifications	n	Per cent
Female pseudohermaphroditism	52	50.0
True hermaphroditism	5	4.8
Male Pseudohermaphroditism	47	45.2
Total	104	100

RESULTS

From 1979 to 2001, a total of 109 ambiguous genitalia patients came to the service. Of these, the authors were able to obtain adequate information in 104 patients, five patients did not have notes available or were lost to follow-up before diagnosis was completed. Table 1 summarizes patient diagnostic categories.

1. Female pseudohermaphroditism

This accounted for 50 per cent or 52 patients. All of them belonged to a form of congenital adrenal hyperplasia. Characteristics of the patients in female pseudohermaphroditism group are shown in Table 2.

Surgical reconstruction: 34 out of 52 patients (65%) underwent clitoroplastic procedures at an average age of 4.4±3.3 years (range 0.1-16.9 years). For vaginoplasty, 19 of 52 patients (36%) underwent one of these procedures at the average age of 6.02±3.9 years (range 1.6-16.9 years).

2. Male pseudohermaphroditism and true hermaphroditism

There were 52 patients in the group which combined male pseudohermaphroditism and true hermaphroditism (50.0%), summarized in Table 1 and 4. All patients demonstrated palpable gonad(s) on either or both sides ranging from a well-descended scrotal testis to one palpable at the external inguinal ring. Of these patients, 41 (78.8%) were initially assigned as males, and 11 patients (21.2%) were assigned as females after birth. In at least two patients (3.8%), for whom information was available, sex reassignment was requested by the parents and was subsequently undertaken. A boy was reassigned at the age of two years and a girl was reassigned at the age of 16 months.

2.1 Gonadal differentiation disorders: the two variations included

2.1.1 True hermaphroditism

Five patients were in this diagnostic category. All had histological evidence of gonadal tissue of both sexes except one (patient 5 in Table 3) who was awaiting surgery. Based on strong clinical grounds, the authors thereby included this patient into this group. Clinical phenotypes of true hermaphrodites are illustrated in Table 3.

2.1.2 Dysgenetic male pseudohermaphroditism

Nine patients with gonadal dysgenesis, who carried 46,XY karyotype were included into this

Table 2. Characteristics of female pseudohermaphrodites.

Etiology	n	%	Age at diagnosis (months)	Initial female sex assignment	%	Initial male sex assignment	%
Congenital adrenal hyperplasia							
• 21 hydroxylase deficiency (n=51)							
Salt wasting	31	60.7	1.77 ± 3.06	29	93.5	2	6.5
Simple virilizer	19	37.2	64.47 ± 30.17	18	94.7	1	5.3
Non-classical	1	1.9	75	1	100		
• 11 β-hydroxylase deficiency (n=1)			N/A	1	100		
Total	52	100					

Table 3. Characteristics of true hermaphrodites in our study.

Patient	Chromosome	Gonads		Tissue diagnosis		Internal sex organs	Response to testosterone	Sex assignment	Surgery	Age of surgery
		Right	Left	Right	Left					
1	46,XX/48,XXYY	Inguinal	Not palpable	ND	Ovotestis	Normal uterus, vagina	ND	Female	Clitoroplasty and vaginoplasty	21 mo
2	46,XX	Scrotal	Inguinal	ND	Ovotestis	R testis, immature uterus and vagina Remnant of fallopian tubes	Penile length from 2.5 cm to 2.8 cm	Male	L gonadectomy and hysterectomy	40 mo
3	46,XY	Scrotal	Inguinal	Testis	Ovary	No Müllerian structure, no vagina	Penile length from 2.0 to 3.3 cm	Male	L gonadectomy & R gonadal biopsy	5 mo
									1° stage repair hypospadias	13 mo
4	46,XX/ 46,XY	Scrotal	Inguinal	ND	Ovotestis	R testis, no uterus, no vagina	Penile length from 2.3 to 3.3 cm	Male	L gonadectomy	15 mo
									1° stage repair hypospadias	19 mo
									2° stage repair hypospadias	52 mo
5*	46,XX	Scrotal	Scrotal	ND	ND	Müllerian duct present	ND	Male	ND	awaiting

Abbreviation: ND, not done; R, right; L, left

* Highly likely to have true hermaphroditism but awaiting exploratory surgical procedure

group. They could be further sub-categorized into many disorders as shown in Table 4.

2.2 Disorders affecting testicular response to hCG and intrinsic enzymatic defect in the testis

There were eight patients in this category; one proved to have congenital lipoid hyperplasia clinically and biochemically, yet awaits a mutational analysis to confirm. The other seven failed to respond to hCG stimulation, in the light of no identifiable Müllerian structure, therefore, they could have either one of the two diagnoses aforementioned.

2.3 Defects in androgen dependent target tissue

Twenty two patients fell into this group of heterogeneity. Failure of target tissues to respond to androgens can stem from either end-organ resistance to androgens (Androgen insensitivity syndrome (AIS; partial or complete forms) or a testosterone metabolism defect at the target tissues, also known as 5 α-reductase deficiency. Normal to elevated levels of testosterone in the face of no Müllerian structures are the basis of grouping these patients together. Long term follow-up when these patients reach adolescence may provide some clues as to the diagnosis since 5 α-reductase deficiency patients become markedly virilized if the gonads are not removed during the prepubertal period.

2.4 Others

An unidentifiable cause of male pseudohermaphroditism occurred in eight patients. Of these, five patients had an incomplete diagnostic work up, as they were lost to follow-up. Three patients had ambiguous genitalia associated with multiple congenital anomalies and Intrauterine growth retardation (IUGR), in the context of 46,XY chromosomal finding. These anomalies included a renal abnormality and blindness in one patient, microcephaly and symmetrical IUGR in two patients.

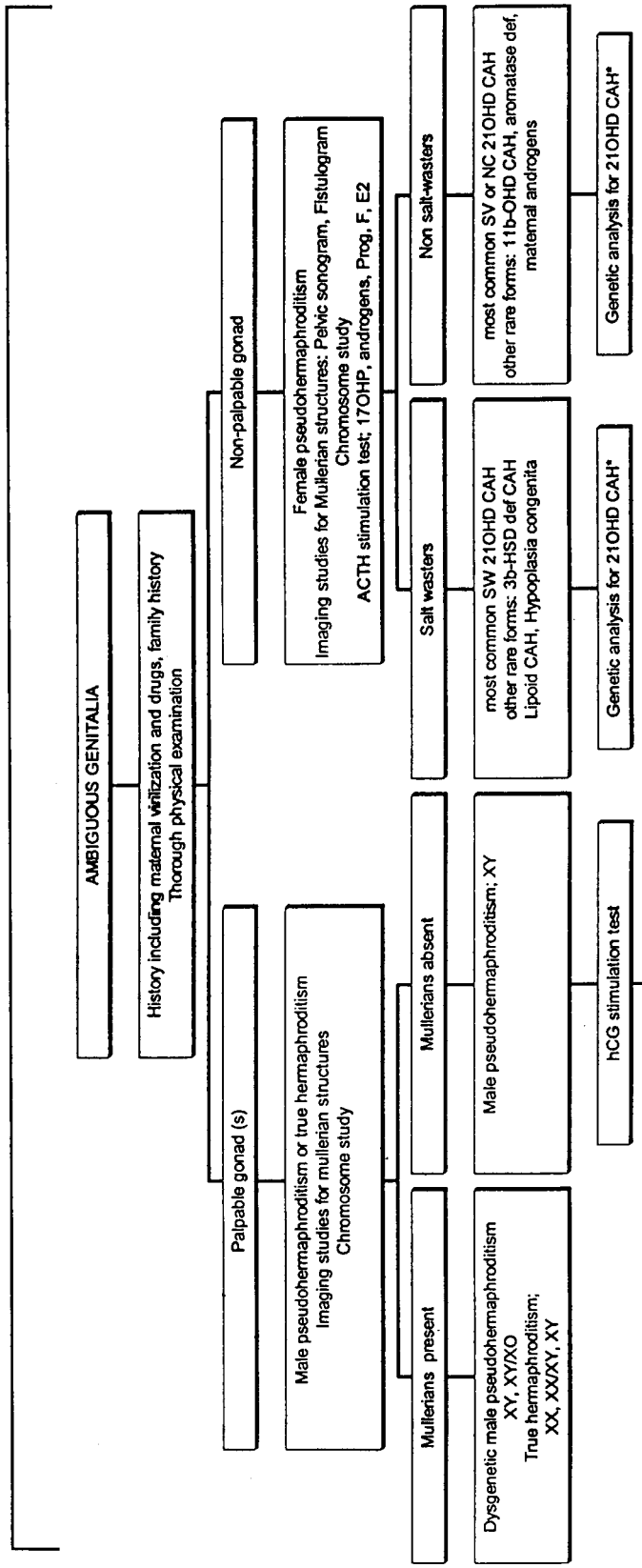
DISCUSSION

Over the past twenty-two years, a total of 104 patients with ambiguous genitalia for whom information was available were under care at the Department of Pediatrics, Siriraj Hospital. Instead of classifying individuals with hermaphroditism according to their gonadal morphology, the authors opted to modify the classification developed by Grumbach and Conte[6,12] in an attempt to blend etiologic mechanisms and clinical entities into a simplified rational classification resulting in proper management and advice to patients with sexual ambiguity (as summarized in Fig.1). The patients are initially categorized with regard to their palpable gonads. When gonads are not palpable, investigation will direct towards female pseudohermaphroditism, in which androgen excess associated with any form of congenital adrenal hyperplasia is the only identifiable cause in genetically female patients, the majority of which is 21 OHD. This is in concordance with other worldwide reports showing that 21 hydroxylase deficiency accounts for more than 95 per cent of CAH[17-20]. Presenting symptoms

Table 4. Male pseudohermaphrodites and their sex assignments.

Disorders	n	Sex assignment	
		Male	Female
Dysgenetic male pseudohermaphrodites			
• Testicular regression syndrome	1	1	
• Campomelic dysplasia	1	1	
• Mixed gonadal dysgenesis	4	4	
• Incomplete gonadal dysgenesis	3	2	1
Testosterone synthetic defect or unresponsiveness to LH/hCG	8*	3	5
AIS or 5 α-reductase deficiency	22	19	3
Unidentified cause	5	4	1
Associated with anomalies	3	3	
Total	47	37 (78.7%)	10 (21.3%)

AIS, Androgen insensitivity syndrome; LH, lutinizing hormone; hCG, human chorionicgonadotropin
* one patient in this group turned out to have stAR deficiency (congenital lipoid hyperplasia)



Abbreviation: 17 OHP, 17 hydroxyprogesterone; Prog, progesterone; F, cortisol; E2, Estradiol; SW, salt wasting; SV, simple virilizing; NC, non-classical; CAH, congenital adrenal hyperplasia; 21OHD, 21 hydroxylase deficiency; 3β-HSD def, 3β-hydroxysteroid dehydrogenase deficiency, 11β-OHD, 11b-hydroxylase deficiency; 17OHD, 17 hydroxylase deficiency.

* Genetic analysis of 21 OHD CAH is now available in our service.

Fig. 1. Siriraj diagnostic decision tree of ambiguous genitalia.

of salt and water loss secondary to aldosterone deficiency among salt wasters such as vomiting, dehydration and weight loss aid in distinguishing it from the non-salt wasting counterpart. The present data showed that salt wasters were diagnosed much earlier than those with non-salt wasting. This is probably due to the more severe enzymatic impairment in salt wasters that causes aldosterone deficiency and life threatening conditions of severe electrolyte and fluid imbalances that, therefore, cause these patients to seek medical attention at a much earlier age. This finding may have an impact on the timing of sex misassignment reversal since it is advised that sex reassignment should not occur after infancy to minimize the risks of psychosocial and psychosexual problems in future life[13,21].

In these individuals, female sex assignment is almost always the case, since they have intact internal female machinery to become mothers and the likelihood of excessive androgen normalization with treatment. There has been a tendency to perform surgical reconstructive procedure earlier in life based on the observations of great psychological stress in untreated patients having the procedure done late in life[13]. In the present cohort, where data was available, the average age of clitoroplasty was 4.4±3.3 years (range 0.1 to 16.9 years) and of vaginoplasty was 6.02±3.9 years (range 1.6-16.9 years), both were well very early in the prepubertal ages.

On the other side of the diagnostic flowchart, individuals with palpable gonad(s) suggests the presence of testicular tissue. Various forms of male pseudohermaphroditism and true hermaphroditism can be filled into the diagnostic framework. In order to classify gonadal differentiation disorders (either dysgenetic testis or true pseudohermaphroditism), in which Müllerian Inhibiting Substance (MIS) from dysgenetic Sertoli cells was also defective, from other forms of male pseudohermaphroditism, imaging studies of the internal sex organ are warranted. Computerized tomographic scan, magnetic resonance imaging or the most commonly used, sonographic study of the pelvis are the options one may utilize to identify Müllerian structures. However, there are drawbacks and limitations to each of these methods of imaging that clinicians need to bear in mind when interpreting the results[22].

Absence of Müllerian structures; namely a uterus, fallopian tubes, or the upper one third of a vagina, with an adequate imaging technique leads to a diagnosis of testosterone action deficiency. These groups encompass defects at the level of LH/hCG receptor, intrinsic testicular enzymatic defects in testosterone production and impairment of androgen dependent target tissue. An hCG stimulation test can be performed to evaluate testicular efficacy in producing testosterone and its potent metabolite, dihydrotestosterone, which can be measured in serum. Unfortunately, due to the limitations of resources, the furthest the authors subcategorize patients was as responders or non-responders. Further sub-categorization of responders as AIS or 5 α reductase deficiency and of non-responders as hCG/LH unresponsiveness or testosterone synthetic defect could-not be accomplished. Impaired testosterone production encompasses one of the three enzymatic defects; 3β-hydroxysteroid dehydrogenase (HSD), 17 hydroxylase, 17,20 lyase or alas 17 HSD deficiency. Each of these has associated findings which can be used as clues to diagnosis, i.e. 3β HSD deficiency has severe salt wasting and 17 hydroxylase has low renin hypertension in addition to undervirilized male characteristics.

In the present cohort, the diagnostic group of either AIS or 5 α reductase deficiency, identified as hCG responders was found to be the most common etiology. This finding, to a certain extent, could be overestimated because the authors included any patient who responded to hCG and no identifiable Müllerian structure into this group. Imaging studies may not yield the same sensitivity as an exploratory procedure, that fewer patients underwent, in identifying Müllerian structures as in other studies. Further, rising of testosterone after hCG is not exclusively found in this diagnostic category. Some patients with gonadal differentiation disorders can produce similar effects especially when there is no standardized threshold. However, patients who could produce a significant rise in testosterone and an increment in phallic size after childhood LH receptor stimulation are more likely to accomplish adequate virilization when the physiological LH pubertal signal arises.

In classical terminology, a true hermaphrodite is a person who possesses both ovarian and testicular tissue. An aggressiveness in performing laparotomy for any patient that did not fit conclusively into a biochemically determined diagnosis boxes might contribute to the disparity in incidences [2]. True hermaphrodites in this study carried various chromosome constituents, 46,XX being the most

common, but others were also found. Hence, a 46, XX karyotype, does not guarantee absence of testicular structure. This finding further emphasizes the importance of a thorough physical examination for a palpable gonad along its passage from the internal ring outwards. In many cases, lubricating the area with soap eased out and increased the yield of the gonad appreciation. Of interest, the majority of true hermaphrodites in this study were reared as males. This is not in line with a larger cohort reported elsewhere[2]. Long-term outcome of these patients, especially their pubertal development will be very interesting to follow.

The management is contingent on the age at diagnosis and assessment of the functional capacity of the internal and external genitalia. The potential psychosexual function of the child has a strong impact on gender assignment, not decisively affected by either karyotype or gonadal mix. The internal organs were either compatible with the gender designation based on the appearance of its own genitalia, or could be changed accordingly[12, 13]. Overall, in the present large cohort of patients, sex reassignment occurred in a relatively low percentage (4.8%) and occurred before the age of 30 months in all but one patient which took place after the age of 30 months. This small percentage can be attributed to the strict guidelines for sex assignment to avoid the tragic outcome suggested by Money et al[23].

With proper assignment of sex for rearing and appropriate continued management with an emphasis on continuity of care, individuals with ambiguous genitalia should be able to lead well-adjusted lives and ultimately a satisfactory sex life. The detection of genital ambiguity in a newborn infant can be seen as a neonatal psychosocial emergency. Once the sex of rearing is assigned, the gender role is thereafter reinforced by appropriate employment of whatever surgical, hormonal, and psychological measures are indicated.

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การศึกษาภาวะอวัยวะเพศกำกวมในผู้ป่วยเด็กและแนวปฏิบัติในการวินิจฉัยของภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล : ประสบการณ์ 22 ปี†

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การวินิจฉัยและการดูแลรักษาผู้ป่วยที่มาพบแพทย์ด้วยภาวะอวัยวะเพศกำกวมจัดเป็นสิ่งที่ยากและท้าทายต่อความสามารถของแพทย์ผู้ให้การดูแลรักษาเด็ก เพื่อที่จะหลีกเลี่ยงผลกระทบต่อร่างกาย จิตใจ และการปรับตัวเข้ากับสังคมรอบข้างของผู้ป่วย วัตถุประสงค์ของการศึกษาในครั้งนี้ เพื่อรวบรวมและแสดงให้เห็นถึงลักษณะทางคลินิกอันนำไปสู่การวินิจฉัยโรคขั้นสุดท้ายของผู้ป่วยภาวะอวัยวะเพศกำกวมที่มารับการรักษาที่หน่วยต่อมไร้ท่อ ภาควิชากุมารเวชศาสตร์ โรงพยาบาลศิริราช ในช่วง 22 ปีที่ผ่านมา นอกจากนั้นยังจะได้นำเสนอขั้นตอนรายละเอียดที่นำไปสู่การวินิจฉัยโรค เป็นวิธีที่ใช้ในหน่วยต่อมไร้ท่อของเรา เพื่อเสนอเป็นแนวทางปรับใช้ในการดูแลผู้ป่วยอวัยวะเพศกำกวมในเวชปฏิบัติ ตั้งแต่ปี พ.ศ. 2522 จนถึงปี พ.ศ. 2544 มีจำนวนผู้ป่วยที่มาด้วยอวัยวะเพศกำกวมจำนวนทั้งสิ้น 109 คน ในจำนวนนี้มี 104 คนที่สามารถนำเวชระเบียนมาศึกษาได้ ผู้ป่วยกลุ่มนี้แบ่งออกได้เป็นผู้ป่วยกะเทยเทียมเพศหญิง 52 คน (50%) ผู้ป่วยกะเทยแท้ 5 คน (4.8%) และผู้ป่วยกะเทยเทียมชาย 47 คน (45.2%) ผู้ป่วยกะเทยเทียมเพศหญิงทั้งหมดมีสาเหตุมาจากภาวะต่อมหมวกไตทำงานพร่องแต่กำเนิดทำให้มีขนาดโต (congenital adrenal hyperplasia) และ ได้รับการเลี้ยงดูเป็นเด็กหญิง การขาดเอนซัยม์ 21 ฮัยดรอกซีเลส (21 hydroxylase deficiency) พบได้ใน 51 คนของผู้ป่วยกลุ่มนี้ สำหรับในกลุ่มผู้ป่วยกะเทยเทียมเพศชาย 47 คนนั้นสามารถแบ่งย่อยออกตามการวินิจฉัยได้เป็น กะเทยเทียมเพศชายอันเกิดจากต่อมเพศพัฒนาผิดปกติ 9 คน (19.1%) การสร้างฮอร์โมนเพศชายผิดปกติ หรือการไม่ตอบสนองต่อฮอร์โมน เอชซีจี (hCG) 7 คน (14.9%) ภาวะดื้อต่อฮอร์โมนเพศชาย หรือภาวะพร่องของเอนซัยม์ 5 แอลฟารีดักเตส (5 α-reductase deficiency) มีจำนวน 22 คน (46.8%) อีก 4 คน (8.5%) มีภาวะอวัยวะเพศกำกวมในผู้ป่วยชายที่มีโครโมโซม 46,XY ร่วมกับความพิการของร่างกายอื่น ๆ และกลุ่มสุดท้ายจำนวน 5 คน (10.6%) ที่ไม่สามารถระบุสาเหตุอันชัดเจนได้ การสลับเพศในการเลี้ยงดูเกิดขึ้นในผู้ป่วยกลุ่มกะเทยเทียมเพศหญิง 4 คน (7.6%) และอย่างน้อยอีกจำนวน 2 คน (3.8%) ในกลุ่มผู้ป่วยกะเทยเทียมเพศชายและกะเทยแท้รวมกัน จากผลการรวบรวมของผู้ศึกษาแสดงให้เห็นว่า พิสัยของปัญหาในเรื่องอวัยวะเพศกำกวมมีไม่น้อย ความไม่เหมาะสมถูกต้องในการจัดการกับปัญหานี้ จะเพิ่มความเสี่ยงต่อทั้งสุขภาพโดยรวมทั่วไป และสุขภาพจิตในอนาคตของผู้ป่วยเด็กกลุ่มนี้

คำสำคัญ : อวัยวะเพศกำกวม, กะเทยเทียมเพศหญิง, กะเทยเทียมเพศชาย, กะเทยแท้, ต่อมหมวกไตทำงานพร่องแต่กำเนิด, ต่อมเพศหญิงพัฒนาผิดปกติ, เอชซีจี, ผลการรักษาระยะยาว

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