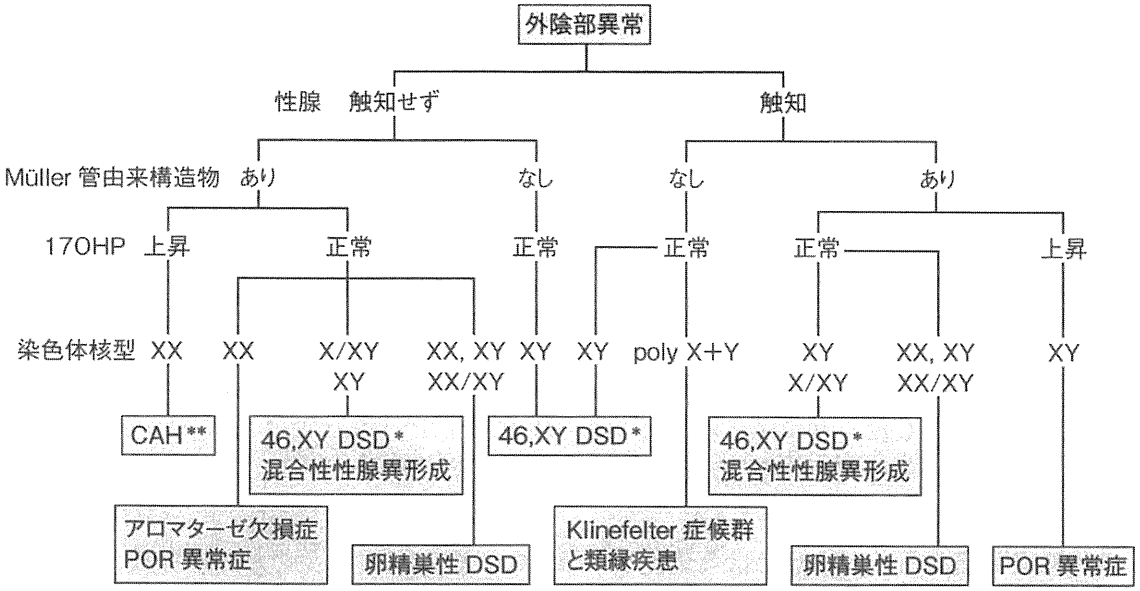

図 1　性分化疾患診断のアルゴリズム（日本小児内分泌学会性分化委員会作成）

* 46,XY DSD：図 2 に続く。** CAH：21 水酸化酵素欠損症，3β水酸化ステロイド脱水素酵素欠損症，11β水酸化酵素欠損症，POR 異常症

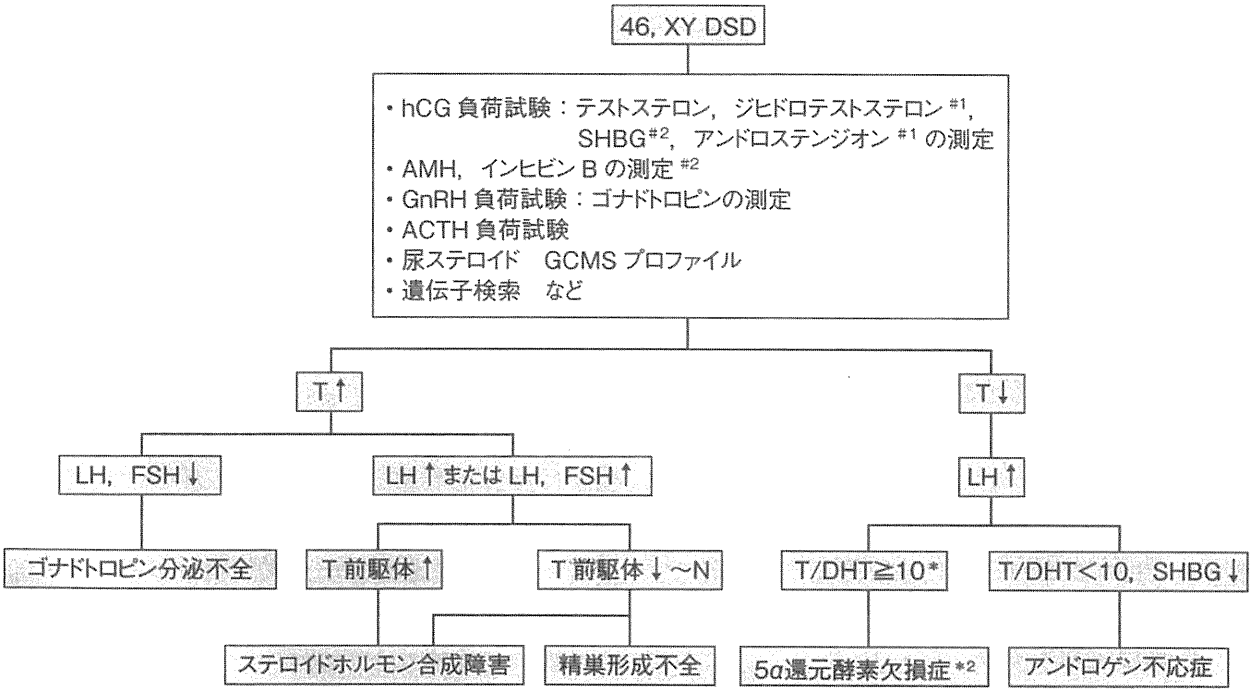

図 2　46,XY 性分化疾患の診断のアルゴリズム

* 基準値はないので参考値。年齢によって測定系の問題（胎児副腎産物との交差）があるので注意を要する。

*2 生化学的には早期診断が困難であるので，確定診断には遺伝子診断が必要である。

#1 保険未収載だが鑑別のために測定が望ましい。

#2 保険適用となっておらず，測定可能施設も限られるため，必須の検査ではない。

46,XY-5α 還元酵素欠損はまれな疾患で，外性器の男性化が不完全で，女性型に近い場合が多い。胎児期に高濃度のテストステロンに曝露されており，脳の性分化は男性に傾いている。最近，女性として成育した本症の多くが男性に性転換しているとの報告が散見されており，外性器の形状だけでは性判定が困難な疾患である。

日本小児内分泌学会性分化委員会（委員長：大

山建司）が作成した性分化疾患診断の手順を図1，2に示す。新生児期においては，戸籍上の性の決定が最も緊急な課題であり，そのための検査を優先する必要がある。性分化疾患を疑い，先天性副腎過形成症が否定された場合は，経験豊富な施設と緊密に連携して，検査，診断，治療方針の決定，性判定を行うべきである。

II 保護者への初期対応

出生直後の説明は，親に強い印象を残すため言葉を選んで，ていねいにくり返し行う必要がある。また，説明内容を統一するため，説明者を決めておいたほうがよい。出生時，親や家族の関心は，5体満足か，男か女か，にほぼ限定されている。本来祝い事であるはずの出生の瞬間に，「男の子か女の子かわからない」，「外陰部に異常がある」などと言われると，親はそれだけで動転してしまう。「わからない」，「異常」，「不完全」という言葉は使うべきではないと考えている。性別がわからないと言うと，子ども自体が男でも女でもない，ととられる可能性がある。説明は母親だけにするのは避け，両親に，または祖父母を加えた場で行う。以下は初期対応の説明の1例である。

「外性器の成熟が遅れていて，性分化疾患が疑われます。性分化疾患とは，卵巣・精巣や性器の発育が非典型的となる疾患です。外性器からは性別を正確に判断できないので検査をしましょう」。

最初の段階で担当医は，印象を受けた性を安易に告げることは避けねばならない。最終的に，性を変更するようなことになると，親を混乱させるだけでなく，周囲への影響もあり，問題を複雑化してしまう。

児の問題点が性分化に関わることだけであれば，ほかの機能は健常であることを積極的に伝え，祖父母にも児の状態を説明して理解を求め，両親を支援するように促す。家族内で責任論が起きないように注意し，とくに精神的に不安定な状態にある母親への配慮，支援が大切である。そのためには，医師以外に病態をよく理解している心理療法士，助産師などの協力も必要となる。

今後の見通しについても説明する必要がある。検査には1週間以上かかること，2週間以内に結果が出せるように努力すること，出生届は急いで出す必要がないこと，2週間では結論が出なくても性・名前は保留できること，医療保険も性・名前保留で提出可能なこと，を説明する。

説明は出生時だけではなくくり返し行い，性分化疾患への理解を深めるように努め，心理カウンセリングの介入も早期から始める。

以上が出生7日目までの初期対応の概略である。経験の少ない医師が性分化疾患に遭遇したとき，すべて一人で対応しようと考えるのではなく，必ず経験豊富な小児内分泌または小児泌尿器の医師に相談すべきである。性分化疾患は同一の疾患であっても症状，検査所見はさまざまであり，診断名から性別を判断することはできない疾患である。長期にわたるフォローが必要であり，安易な対応は厳に慎まなければならない。

Key Points

❶出生時，外性器の形状を詳しく観察する習慣をつける。
❷外性器異常を疑ったときは，必ず経験豊富な医師に相談する。
❸親への初期対応，とくに言葉使いは慎重を要する。
❹先天性副腎過形成症以外の性分化疾患では，経験豊富な施設への転送をためらわない。

文 献

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Acquired Undescended Testes in Boys With Hypospadias

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Abbreviations and Acronyms

CGRP = calcitonin gene-related peptide

GFN = genitofemoral nerve

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Purpose: We determined the incidence of acquired undescended testes in boys with hypospadias.

Materials and Methods: We retrospectively reviewed the records of 566 boys with hypospadias who were referred to our outpatient clinic between January 2000 and September 2009. Acquired undescended testes were defined as testes that were documented at the bottom of the scrotum at least once after birth by the pediatric urologist at our institution but were subsequently documented to have moved from a satisfactory scrotal position by the same pediatric urologist or an equally experienced pediatric urologist. However, this definition did not include undescended testes after inguinoscrotal surgery. We excluded boys with gender development disorders with testicular dysgenesis, those who underwent bilateral inguinoscrotal surgery and those without congenital cryptorchidism who were followed less than 3 months.

Results: Of the 566 boys with hypospadias 100 met study exclusion criteria. Of the 466 boys included in analysis 29 (6.2%) had congenital cryptorchidism and 15 (3.2%) had acquired undescended testes. Urethroplasty was performed in 413 boys, including 91 with distal, 132 with mid and 181 with proximal hypospadias. The incidence of congenital cryptorchidism and acquired undescended testes in boys with proximal hypospadias was significantly higher than that in boys with other types of hypospadias ($p = 0.03$ and 0.001, respectively).

Conclusions: Boys with proximal hypospadias are at a higher risk for acquired undescended testes than those with other mild types of hypospadias. Thus, testicular location should be monitored regularly until after puberty.

Key Words: testis, cryptorchidism, hypospadias, abnormalities

In clinical practice acquired undescended testis is occasionally observed in boys with hypospadias. The pathological factors of hypospadias may include disruption of androgen and the androgen regulated inguinoscrotal phase of testicular descent.[1–3] Theories on the mechanism of testicular ascent remain controversial. Tasian et al reported that proximal hypospadias is associated with acquired undescended testes.[4] However, it is unclear whether distal and middle hypospadias carry a similar risk. We present what is to our knowledge the first study to determine the incidence of acquired undescended testes according to hypospadias severity.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of 566 boys with hypospadias who were referred to our outpatient clinic between January 2000 and September 2009. We excluded 100 boys from study, including 18 with gender development disorders

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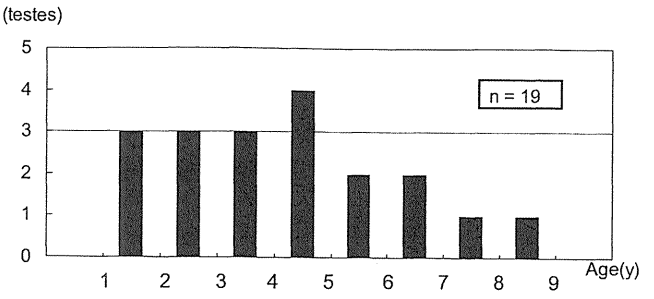
with testicular dysgenesis, eg mixed gonadal dysgenesis and true hermaphroditism, 24 who underwent bilateral inguinoscrotal surgery and 58 without congenital cryptorchidism who were followed less than 3 months. A total of 466 boys were included in the analysis.

We defined the distal type as glanular, coronal and subcoronal hypospadias, the mid type as distal penile, mid shaft and proximal penile hypospadias, and the proximal type as penoscrotal and more proximal hypospadias. We ascertained testicular position, age at the diagnosis of acquired undescended testes and orchiopexy findings. An acquired undescended testis was defined as a testis that was documented to be at the bottom of the scrotum at least once after birth by the pediatric urologist at our institution but was subsequently documented to have moved from a satisfactory scrotal position by the same pediatric urologist or an equally experienced pediatric urologist. However, this definition did not include undescended testes after inguinoscrotal surgery. Followup was considered complete if bilateral orchiopexy or inguinoscrotal surgery was performed. Statistical analysis was performed using the chi-square test with $p < 0.05$ considered significant.

RESULTS

A total of 466 boys were included in this study. Mean age at the initial visit was 1.1 year (range 0 to 12.8) and mean followup was 42.4 months (range 3 to 123). Of the 466 boys 29 (6.2%) had congenital cryptorchidism and 15 (3.2%) had acquired undescended testes. Primary urethroplasty was done at our institution in 413 boys, including 181 with proximal, 132 with mid and 91 with distal hypospadias. Another 26 boys underwent primary urethroplasty elsewhere and 27 did not undergo urethroplasty. Of the 181 boys with proximal hypospadias 15 (8.3%) had congenital cryptorchidism and 12 (6.6%) had acquired undescended testes. Six of the 132 boys (4.5%) with mid hypospadias had congenital cryptorchidism and 2 (1.5%) had acquired undescended testes. Two of the 91 boys (2.2%) with distal hypospadias had congenital cryptorchidism and none had acquired undescended testes. The incidence of congenital cryptorchidism and acquired undescended testes in boys with proximal hypospadias was significantly higher than in boys with other types of hypospadias ($p = 0.03$ and 0.001, respectively). In 15 boys (19 acquired undescended testes) mean age at diagnosis was 4.3 years (range 1.3 to 8.5 years) (see figure). We performed a total of 17 orchiopexies in 13 boys with acquired undescended testes. Of the testes 12 (70.6%) were at an extracanalicular site, 3 (17.6%) were in the superficial inguinal pouch, 2 (11.8%) were intracanalicular and none was intra-abdominal.



Patient age at diagnosis of acquired undescended testes

DISCUSSION

In 1966 Vellumsen and Zachau-Christiansen reported that 69 of 4,300 boys (2%) showed unilateral or bilateral ascent of the testes from the normal scrotal position at birth by age 3 years.[5] Since then, many reports have described acquired undescended testes. Retrospective analysis of the scrotal position of testes reported by other physicians is common but the accuracy of previous examinations cannot be confirmed. Some reports may have included patients in whom a retractile testis was misdiagnosed as an acquired undescended testis. Discrepancies in the incidence of acquired undescended testes have been noted in different reports and, thus, its true incidence remains controversial. In reports of patients who were followed for a long period and in whom the previous testicular position was substantially documented boys with apparent testicular ascent represented 2% to 20% of all who underwent orchiopexy.[6–8] Conversely the orchiopexy rate is as high as 2% to 3% in all males up to ages 14 to 17 years despite an expected childhood prevalence of congenital cryptorchidism of approximately 1%.[9–14] Thus, the generalized incidence of acquired undescended testes is estimated to be 0.04% to 0.6%.

Our results show that the incidence of congenital cryptorchidism and acquired undescended testes in boys with hypospadias was 6.2% and 3.2%, and the incidence of these types of testicular maldescent in patients with proximal defects was 8.3% and 6.6%, respectively. These conditions were predominantly observed in boys with proximal defects ($p = 0.03$ and 0.001, respectively) while the incidence of congenital cryptorchidism was 2.2%. To our knowledge acquired undescended testes have not been reported in boys with distal defects.

It was previously reported that congenital cryptorchidism is predominant in boys with proximal hypospadias.[15] We observed that acquired undescended testes was also predominant in such boys. Tasian et al reported that proximal hypospadias is associated with acquired undescended testes[4] but it is unclear whether distal and mid hypospadias carry a similar risk. To our knowledge we report

the first study showing that the risk of acquired undescended testes increases directly with hypospadias severity.

Ethnic characteristics may be a reason why the incidence of acquired undescended testes was higher in the study by Tasian et al[4] than in our series. Of their study patients 48.7% were white and 15% were Asian. However, all patients in our study were Japanese, ie Asian. The overall incidence of distal, mid and proximal hypospadias in white boys is approximately 50%, 30% and 20%, respectively.[16] On the other hand, proximal hypospadias is predominant in Japanese boys. In our study the overall incidence of distal, mid and proximal hypospadias was 22%, 32% and 44%, respectively. Thus, similar to the difference in the incidence of proximal hypospadias in the 2 races, there is a difference in the incidence of acquired undescended testes.

Barthold and Gonzalez reported data[17] from reviews of patients with substantial documentation of acquired undescended testes.[6,8,18–23] Mean age at diagnosis was 6.6 to 8.1 years and the most common testicular site identified at orchiopexy was distal to the inguinal ring. In our series mean age at diagnosis in boys with hypospadias was 4.3 years, which is lower than that in the unselected acquired undescended testes series reviewed by Barthold and Gonzalez.[17] We observed the same testicular site, identified at orchiopexy, as that reported by Barthold and Gonzalez. Since details on the processus vaginalis and gubernaculum, and testicular pathology were unavailable, we could not analyze these parameters.

Theories on the mechanism of testicular ascent remain controversial but some mechanisms have been proposed to explain this phenomenon. A theory is that a fibrous remnant of the processus vaginalis remains tethered to the testis and peritoneum, and can pull the testis up into the inguinal canal during growth.[20,22] Cremaster muscle spasticity is a possible cause of acquired undescended testes, eg in patients with cerebral palsy, but the proposed etiology of this spasticity in otherwise normal boys is unclear.[24] In this study neither cerebral palsy nor myopathy was observed in the 15 boys with acquired undescended testes. The GFN may have a role in testicular ascent. Hutson and Hasthorpe proposed that the GFN acts as a second messenger for androgen by releasing CGRP to control descent.[3] Shono et al reported that the proximal division of the GFN in neonatal rats causes inguinoscrotal testicular maldescent and may also induce testicular ascent in adulthood.[25] They proposed that testicular ascent may be caused by some intrauterine disorders of the GFN.

To our knowledge a relationship between acquired undescended testes and hypospadias has not yet been reported. It is not clear why boys with hypospadias are at high risk for acquired undescended testes. Nazir et al reported that compared with the normal prepuce the hypospadiac prepuce is hypo-innervated for CGRP positive nerves.[26] Androgen disruption caused by hypo-innervation of CGRP positive nerves may be responsible for the high incidence of acquired undescended testes in boys with hypospadias.

Previous studies of acquired undescended testes indicate that these testes show germ cell maldevelopment, similar to that in age matched patients with congenital cryptorchidism.[8,21,24] Orchiopexy is commonly recommended for acquired undescended testes.[27] At our institution orchiopexy is done soon after the diagnosis of acquired undescended testes. Conversely Sijstermans et al reported that acquired undescended testes have a high tendency of spontaneous descent during early and mid puberty, and orchiopexy may be recommended during mid or late puberty in cases of nondescent.[28] Thus, more comprehensive data on the natural course of acquired undescended testes and on testicular growth after orchiopexy are urgently required.

The limitations of this study are similar to those of other retrospective reviews. Followup was short. Longer followup may allow the detection of acquired undescended testes at an older age. Also, approximately 70% of acquired undescended testes cases were diagnosed within the first 5 years in this study. However, Guven and Kogan reported the diagnosis of acquired undescended testes in 14-year-old boys.[29] This pattern indicates that the testicular site in boys with proximal hypospadias should be monitored regularly until after puberty.

CONCLUSIONS

To our knowledge we report the first study to determine the incidence of acquired undescended testes according to hypospadias severity. Since a high incidence (6.6%) of acquired undescended testes was observed in boys with proximal hypospadias only, there may be a strong association between acquired undescended testes and proximal hypospadias. Thus, testicular location should be monitored regularly until after puberty in boys with proximal hypospadias.

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Original Article: Clinical Investigation

Long-term outcome of ovotesticular disorder of sex development: A single center experience

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Objectives: To describe the clinical features of children with ovotesticular disorder of sex development (DSD) and to review cases of ovotesticular DSD in Japan.

Methods: Medical records of eight children diagnosed with ovotesticular DSD at our institute during the past 17 years were retrospectively evaluated. A review of 165 reported cases of ovotesticular DSD from Japanese institutions was carried out.

Results: Mean follow up was 8.2 years for six children, with two children lost to follow up. Mean age at first presentation was 2.4 months. All children were Japanese. The most common initial manifestation was ambiguous genitalia. The female- : male ratio as the sex of rearing was 1:1. Gender reassignment, from male to female, was carried out in one child at 4-months-old. Genital surgery was always carried out in early childhood as per family desire. Appropriate gonadal tissue was preserved except for one child. No gonadal tumors were detected during follow up. Spontaneous pubertal development occurred in one boy. In reviewing Japanese data, the frequency of testes was higher than in other ethnicities and this was related to the higher incidence of 46,XY.

Conclusions: According to our experience, most families in Japan desire early genital surgery in the case of ovotesticular DSD. Chromosomal and gonadal distributions in patients with ovotesticular DSD differ between Japanese and other ethnic groups. Treatment for these patients needs to be provided after considering the cultural and social backgrounds of DSD in Japan.

Key words: follow-up studies, gonads, sex differentiation disorders, treatment outcome, true hermaphroditism.

Introduction

A consensus statement on the management of intersex disorders was published in 2006.[1] The term "true hermaphrodite" has been replaced by ovotesticular disorder of sex development (DSD), defined as the presence in the same individual of ovarian tissue containing ovarian follicles and testicular tissue containing seminiferous tubules.[2] The incidence and constituting karyotype in patients with ovotesticular DSD reportedly show geographic variations.[3] Cultural and social differences in dealing with DSD influence gender assignment and consecutive management.[4] However, there is a paucity of data regarding clinical features, gender assignment and treatment outcomes in children with ovotesticular DSD in Japan.[5] We present herein the clinical, anatomical, histological, cytogenetic and hormonal findings of ovotesticular DSD and assessed gender assignment and treatments for children with ovotesticular DSD treated at our single center. We also reviewed the 165 cases of ovotesticular DSD reported in Japan to date.

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Methods

Eight children at our hospital were diagnosed with ovotesticular DSD between 1991 and 2008. Ovotesticular DSD was defined by histological findings of the gonads. We retrospectively assessed clinical, anatomical, histological, cytogenetic and hormonal data, gender assignment and treatment in these eight children.

Clinical examination included the degree of virilization of the external genitalia according to Prader's classification,[6] and palpation of the gonads in inguinal and labioscrotal areas. Associated malformations were recorded.

Anatomical examination included the position of the gonads, the presence of Müllerian and Wolffian derivatives, and the presence of a urogenital sinus. These findings were ascertained by endoscopy and laparotomy or laparoscopy in all children.

Gonadal tissue was assessed by careful examination and on biopsy sections or resected gonads that were discordant

with the sex of rearing. Tissue specimens were fixed in formalin and embedded in paraffin wax. Paraffin blocks were sectioned and stained using hematoxylin and eosin. Histological evaluation was carried out by one pathologist (MN).

Cytogenetic analysis of karyotype was carried out using peripheral blood in all children. The sex-determining region of the Y chromosome (SRY) gene was studied by fluorescence *in situ* hybridization in all children.

Before surgery, Leydig cell function was evaluated by measuring plasma testosterone (T) concentration before and on days 4 and 5 after stimulation with human chorionic gonadotropin (hCG) at 3000 units/m^2/day given on three consecutive days in all children. Mean age at hCG stimulation was 9.4 months (range 2–27 months). A maximum T concentration after stimulation of >200 ng/dL was defined as a normal response to hCG. Maximum T concentration after stimulation of 100–200 ng/dL was defined as a borderline response to hCG. A maximum T concentration after stimulation of <100 ng/dL was defined as a poor response to hCG with the modification previously reported.[7] After resection of the testicular portion of the ovotestis in children raised as females, the hCG stimulation test was carried out to ensure that no testicular remnant was left.[8]

When we treated children with DSD, we promptly held a meeting of the in-hospital gender assignment committee, which comprises pediatric urologists, endocrinologists, neonatologists and a clinical geneticist. We considered many factors that influence gender assignment, including diagnosis, genital appearance, surgical options, need for lifelong replacement therapy, potential for fertility and social factors. After the meeting, we talked with the patient's family several times and then proposed the gender considered most appropriate for the child with DSD.

Gonadal tissue and duct structures inappropriate to the sex of rearing were removed after histological confirmation and gender assignment. When the gonad was an ovotestis, the appropriate portion was preserved wherever possible (Fig. 1). For children raised as females, clitoroplasty and vaginoplasty were carried out as needed. Clitoroplasty was carried out using Schmid's technique based on the preservation of the neurovascular bundle.[9] For children raised as males, urethroplasty, scrotoplasty and uterocolpectomy were carried out when needed. Penile reconstruction was carried out in a 1-stage operation using a preputial pedicled flap or free skin graft or 2-stage operation. Resection of the vagina was carried out with the preservation of at least one vas deferens for the possibility of spontaneous male fertility. Gonadal surveillance ultrasonography for tumor development was carried out annually.

Pubertal development was evaluated by pediatric endocrinologists. At puberty, hormonal replacement was instituted in cases of androgen or estrogen deficiency.

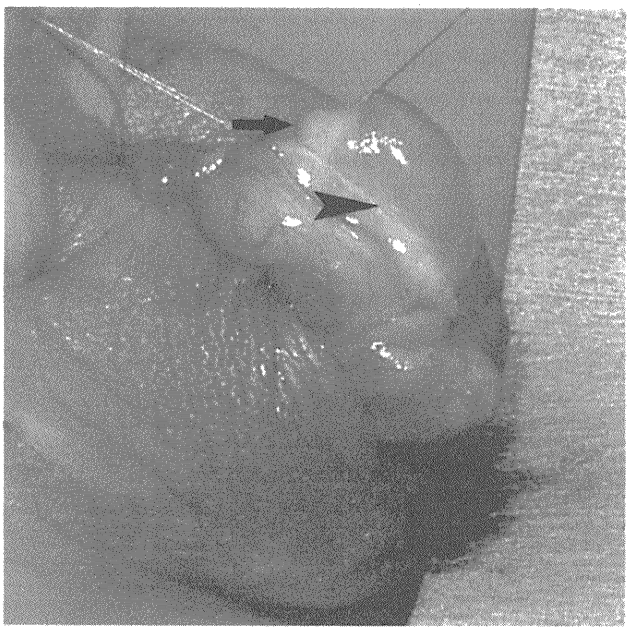

Fig. 1 Macroscopic findings of ovotestis. Ovarian portion (arrow) is firm and yellow in an upper pole, whereas testicular portion (arrowhead) is soft and pink in a lower pole. There is a distinct line of demarcation between the two portions.

We reviewed 165 cases of ovotesticular DSD reported in Japan. Relevant published studies were identified in a database search of PubMed (1966 to January 2010) for articles written in English, and of J Dream II (1981 to January 2010) for articles written in Japanese and references from selected citations.

Data were analyzed using Statistical Package for the Social Sciences statistical software version 14.0 (SPSS, Chicago, IL, USA). Associations between variables were examined using χ^2-test and Mann–Whitney *U*-test. Values of $P < 0.05$ were considered statistically significant.

Results

Clinical, anatomical, histological and cytogenic data

Clinical, anatomical and cytogenic data are shown in Table 1. The mean age at first presentation was 2.4 months (range birth–13 months). Six of the eight children (75%) presented within 1 month. All children were Japanese. All cases were sporadic, with no family history of sexual ambiguity. Initial manifestations were as follows: ambiguous genitalia in four cases (patients 1, 4, 5, 6); isolated clitoromegaly in two cases (patients 3, 8); perineal hypospadias in one case (patient 2); and identification during surgery for cryptorchidism in one case (patient 7). The diagnosis of ovotesticular DSD was made within a month after referral in all except patient 2. Initial manifestation in patient 2 was perineal hypospadias, and bilateral gonads were located in

Table 1 Clinical, anatomical, histological and cytogenetic data for eight children with ovotesticular disorder of sex development

Patient	Age at first evaluation	Karyotype	External genitalia		Urogenital sinus	Prader grade	Vagina	Uterus	Right gonad	Right duct	Left gonad	Left duct	Postoperative gonadal status R/L	Sex of rearing	Age in years
			Right gonad	Left gonad											
1	Newborn	46,XX	NP	Inguinal	−	II	+	+	Streak	Tube	Ovot	Vas	−/−	Female	16
2	Newborn	46,XX	Labioscrotal	Labioscrotal	+	IV	+	Hypo	Ovot	Vas	Ovot	Vas	Testis/testis	Male	13
3	3 weeks	46,XX	NP	Inguinal	−	II	+	+	Ovary	Tube	Ovot	Tube	Ovary/ovary	Female	Lost
4	Newborn	46,XX	Labioscrotal	NP	+	IV	+	+	Ovot	Tube	Ovary	Tube	Ovary/ovary	Male→female	11
5	1 month	46,XX	Labioscrotal	Labioscrotal	+	IV	+	−	Ovot	Vas	Ovot	Vas	Testis/testis	Male	Lost
6	Newborn	46,XY	Labioscrotal	Labioscrotal	+	IV	+	+	Testis	Vas	Ovot	Vas	Testis/testis	Male	3
7	13 months	46,XX/46,XY	Labioscrotal	Inguinal	+	V	+	+	Testis	Vas	Ovot	Vas + tube	Testis/−	Male	3
8	4 months	46,XX	NP	NP	−	II	+	+	Ovot	Tube	Ovot	Tube	Ovary/ovary	Female	3

Hypo, hypoplastic; NP, non-palpable; Ovot, ovotestis; Tube, fallopian tube; Vas, vas deferens.

the scrotum, with a testis-like consistency. The diagnosis of ovotesticular DSD was made 7 years later, after referral when he underwent orchiopexy for ascending testes to an inguinal lesion and the gonads revealed ovotestis. According to Prader's classification, four children were classed as stage IV, three as stage II, and one as stage V. Palpation of labioscrotal and inguinal areas revealed the presence of at least one gonad in seven children. No gonad was palpable in the remaining child. No child showed associated somatic malformations.

A vagina was detected in all children and seven children had a uterus. Gonadal distribution was as follows: bilateral ovotestis in three children (37.5%); ovary plus ovotestis in two children (25%); testis plus ovotestis in two children (25%) and ovotestis plus streak gonad in one child (12.5%). The most frequently seen gonads were ovotestis (68.8%). Ovotestes were generally located on the left side (right, $n = 4$; left, $n = 7$). The adjacent duct was a vas deferens in six gonads, a fallopian tube in four gonads and both vas deferens and fallopian tube in one gonad. Ovaries were located on both sides equally and all adjacent ducts were fallopian tubes. All testes were located on the right side and the adjacent duct was vas deferens. Of the 11 gonads palpated, nine gonads were ovotestis and two were testis. The five gonads not palpated comprised two ovotestis, two ovaries and one streak gonad. All testes were located in the labioscrotal area, while all ovaries were located intra-abdominally.

Histological examination showed all ovarian tissues were normal with primordial follicles and ovarian stroma. Seminiferous tubules were found in all and spermatogonia were found in 11 of the 13 testicular tissues (84.6%). However, only a very small number of spermatogonia was seen in a seminiferous tubule. In some tissues, the density of seminiferous tubules was decreased and interstitial tissue was increased. Increased interstitial tissue was found in descended testicular tissue as well as in undescended testicular tissue. Sertoli cells were found in all cases and Leydig cells were present in three cases (23.1%). No gonadal tumors were found in all gonads.

The most common karyotype was 46,XX (75%). The other karyotypes were 46,XY (12.5%) and 46,XX/XY (12.5%). All six children with 46,XX showed negative results for the SRY gene. A 46,XY child and a 46,XX/XY child had the SRY gene.

Hormonal data

Hormonal data are shown in Table 2. In the three children younger than 6 months, mean basal T concentration was 118.6 ng/dL (range 85–186 ng/dL). For five children aged 6 months and older, mean basal T concentration was 4.8 ng/dL (range 3–8 ng/dL). After hCG stimulation, mean T concentration was 284.2 ng/dL (range 36.5–590 ng/dL).

Table 2 Preoperative testosterone response after human chorionic gonadotropin stimulation for eight children with ovotesticular disorder of sex development

Patient	Plasma testosterone (ng/dL)		
	Basal	After hCG	Response
1	5.0	36.5	Poor
2	8.0	235.0	Normal
3	5.0	188.6	Borderline
4	69.8	508.1	Normal
5	270.0	590.0	Normal
6	98.3	311.1	Normal
7	3.0	283.1	Normal
8	3.0	120.9	Borderline

hCG, human chorionic gonadotrophin.

Five children showed normal response to hCG, two showed borderline response and one showed poor response. No differences were seen in response with or without a Y chromosome (with, 311.6 ng/dL; without, 238.4 ng/dL, not significantly different). Three children raised as females who underwent resection of the testicular portion of ovotestis showed no postoperative testosterone response, with the exception of one female child who underwent a bilateral gonadectomy.

Gender assignment and treatment

Four children (50%) were being raised as girls and four (50%) as boys. Gender reassignment, from male to female, was carried out in one child (patient 4) at 4-months-old, because the child had a capacious vagina, a normal appearing uterus and a unilateral ovary. Six children were followed from 3 to 16 years (mean 8.2 years). Two children were lost to follow up.

Among the four children being raised as girls, three children had a preserved ovary or ovarian portion of the ovotestis. One child (patient 1) underwent a bilateral gonadectomy, as one gonad was a streak gonad and the other ovotestis had no distinct demarcation between ovarian and testicular tissue. All children underwent clitroplasty. One child who had a urogenital sinus underwent vaginoplasty using a perineal skin flap. Mean age at feminizing genitoplasty in combination with partial or total gonadectomy was 15.5 months (range 5–36 months). Among the four children being raised as boys, all children had a preserved testis or testicular portion of the ovotestis. Three children underwent urethroplasty and scrotoplasty. Three children underwent uterocolpectomy. The mean age at partial gonadectomy was 39.3 months (range 12–90 months). Mean ages at urethroplasty and uterocolpectomy were 24 months (range 11–37 months) and 18 months (range 5–31 months), respectively. No gonadal tumors were detected on follow up in all children.

Pubertal development could be assessed in two patients who reached pubertal age. Hormonal replacement was initiated in one girl at 13 years-of-age, as she had undergone a bilateral gonadectomy. She showed breast development at 13 years-of-age and menses at 14 years-of-age. One boy began spontaneous pubertal development at 13 years-of-age, with basal T concentration rising to 202.9 ng/dL. No cases of pregnancy or paternity were encountered.

Table 3 Gonadal combination of 165 patients with ovotesticular disorder of sex development published in the literature in Japan

Gonadal distribution	*n*	%
Ovot – Ovary	56	33.9%
Ovary – testis	40	24.2%
Ovot – ovot	34	20.6%
Ovot – testis	27	16.4%
Ovot – streak	2	1.2%
Others	6	3.6%
Total	165	100.0%

Ovot, ovotestis.

Chromosomal and gonadal distribution, and gender assignment of ovotesticular DSD published in the literature in Japan

Chromosomal analysis was carried out using peripheral blood, gonad or skin fibroblast in 125 cases. A karyotype of 46,XX was the most frequent finding (61.6%), followed by chromosomal mosaicism containing a Y chromosome (24.8%), whereas 46,XY occurred in 12.8% of cases (Fig. 2). The 324 described gonads of 165 cases were distributed as shown in Figure 3. The most common gonad was ovotestis (49.1%), followed by ovary (29.6%) and testis (20.7%). The gonadal combination of ovotestis plus ovary was most common, followed by ovary plus testis, and bilateral ovotestis (Table 3). Patients with a Y chromosome more often had a testis than patients without a Y chromosome (58.3% *vs* 24.7%; $P = 0.0002$). In 142 patients, the sex of rearing was presented. A total of 86 patients (60.6%) were reared as male and 56 (39.4%) as female.

Discussion

Most children with ovotesticular DSD have presented with ambiguous genitalia as neonates or infants. Rarely, ovotesticular DSD is detected later in individuals with normal

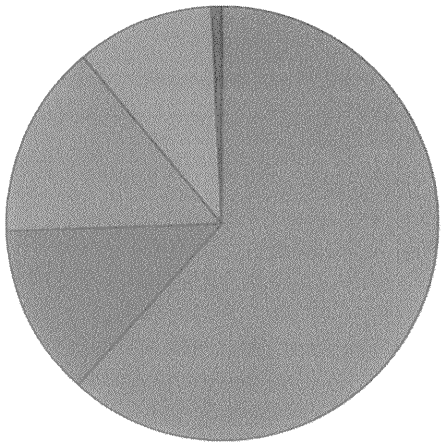

Fig. 2 Chromosomal distribution of 125 patients with ovotesticular DSD published in the literature in Japan. ■, 46,XX (77 patients, 61.6%); ■, 46,XY (16 patients, 12.8%); ■, 46,XX/XY (18 patients, 14.4%); ■, other mosaicism (13 patients, 10.4%); ■, other (1 patient, 0.8%).

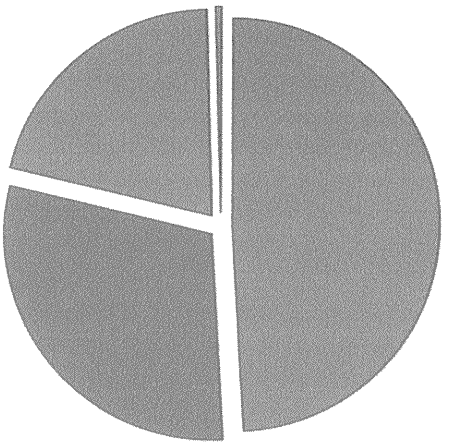

Fig. 3 Gonadal distribution of 324 gonads of a total of 165 patients with ovotesticular DSD published in the literature in Japan. ■, ovotestis (159 gonads, 49.1%); ■, ovary (96 gonads, 29.6%); ■, testis (67 gonads, 20.7%); ■, streak (2 gonads, 0.6%).

female or male phenotype.[10] Actually, in the present study, external genitalia ranged from phenotypically nearly female to normal male.

The most common karyotype was 46,XX, constituting 61.6% of patients in the present study and reviewed cases from Japan. This finding was consistent with the published literature from other countries.[2,3,11] A large review of ovotesticular DSD has shown geographic variations.[3] In the largest review, the 46,XX karyotype was reported as being particularly frequent in South and Western Africa, whereas chromosomal mosaicism containing the Y chromosome is relatively common in Europe and North America, and 46,XY is equally distributed over Asia, Europe and North America.[3] In contrast, the present review showed that the incidence of 46,XY was higher in Japanese than in other ethnicities reported in the literature (12.8% *vs* 7.0%, respectively). The incidence of chromosomal mosaicism in Japan (24.8%) was less than in Europe (40.5%), but was equal to that in North America (21.1%).[3]

Frequency of the SRY gene in children with 46,XX ovotesticular DSD varies in the literature from 0 to 100%.[12,13] The present study showed that no children with 46,XX ovotesticular DSD had the SRY gene in peripheral lymphocytes. Only a few reports from Japan showed the SRY gene in ovotestis in children with 46,XX ovotesticular DSD.[14] In contrast, a study by Ortenberg *et al.* showed the SRY gene in all ovotestes, suggesting that somatic mosaicism might be a cause of 46,XX ovotesticular DSD. However, the exact mechanisms leading to testicular development in SRY-negative ovotesticular DSD remain unclear.

In our review of data from Japan, the most common gonad was ovotestis, followed by ovary and testis as has already been described in other ethnicities.[3,11] However, the frequency of testis was higher in Japan than in other ethnicities (20.7% *vs* 12.5%, respectively).[3] This difference might be explained by the high incidence of the Y chromosome in Japan.

Spermatogonia were found in the present study (84.6%) more than in previous reports (0–67%).[2,3,15,16] This is possibly because most of the children in the present study underwent biopsy before 3 years-of-age. According to previous reports, testicular tissue becomes dysgenetic and germ cells disappear with age.[15,17] The density of seminiferous tubules and interstitial tissue varied quite widely in the present study. This finding was unrelated to the position of testicular tissue or the timing of the operation. Ovarian tissues were normal, with the presence of numerous follicles, as previously reported.[2,3]

Few published data are available for Leydig cell function in children with ovotesticular DSD.[16,17] More than 60% of children showed a normal T response to hCG stimulation in infancy. Response to hCG stimulation did not correlate with the presence of a Y chromosome. However, this finding must be considered in light of the fact that the present study investigated a small series of children with ovotesticular DSD.

The female : male ratio as the sex of rearing was 1:1 in the present study, similar to findings from a previous review.[3,11] Surgery is generally necessary after gender assignment. This includes removal of gonads and internal ducts inappropriate to the sex of rearing, and genitoplasty to construct the appropriate external appearance. However, the timing of surgery remains contentious.[1] Some advocate early surgery to reduce psychological trauma and facilitate acceptance in children and parents.[18,19] Conversely, some patient groups, such as the Intersex Society of North America, advocate deferring the irreversible genital surgery until children are mature enough to make the decision for themselves. According to our 20-year experience in Japan, despite informing

families of all treatment options available, they have often desired early gonadal surgery and genitoplasty. We believe early operations improve the attachment between a child and parents, and benefit the development of gender identity in childhood. Kuhnle and Krahl[4] identified cultural differences as an important factor in dealing with DSD patients. As a result, we carried out gonadal surgery and genitoplasty in early childhood, preserving gonads appropriate to the sex of rearing in 87.5% of children to allow normal pubertal development. On 8.2-year mean follow up, none of these children had gender identity disorder or gender dysphoria.

The frequency of gonadal tumors in patients with ovotesticular DSD has been reported as 2.6–4.6%.[2,3] In the present study, no patients showed gonadal tumors on follow up. Patients with 46,XY and 46,XX/XY ovotesticular DSD tend to develop gonadal tumors more frequently than those with 46,XX ovotesticular DSD.[20] Tumors have been described in both ovarian and testicular portions. The incidence of gonadal tumors increases with age in DSD patients with the Y chromosome.[21] Whether descent of the testis into the scrotum, removal of inappropriate gonads or early surgery influence the occurrence of tumors is unclear.

Some limitations of the present study must be acknowledged. The study involved a small series of patients with ovotesticular DSD and most patients were too young for assessment of sexual and gonadal function. Also, there are no outcome data about gender identity and quality of life in the form of standardized questionnaires. Further studies on long-term follow up are needed to evaluate gender identity, quality of life and sexual function in children with ovotesticular DSD.

We evaluated clinical features, gender assignment and treatment outcomes in children with ovotesticular DSD treated at our institute. According to our experience, most families have desired early gonadal surgery and genitoplasty in Japan. Reviewing data from Japan, chromosomal and gonadal distributions differed between Japanese and other ethnic backgrounds. Consideration of the cultural and social backgrounds of DSD in Japan is needed when providing treatment for children with ovotesticular DSD.

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新規 SF-1 遺伝子変異を認めた副腎不全を伴わない 46, XY DSD の一例

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はじめに

SF-1 は副腎および性腺の発生、分化に必須な核受容体転写因子で、ヒトでは 1999 年に SF-1 の半量不全による 46, XY disorders of sex development (DSD) と副腎不全を発症した症例がはじめて報告され[1]、その後 46, XX の症例[2]、また 46, XY DSD の症例では副腎不全を伴わないものが多く報告されている[3)-6)]。今回我々は副腎不全を伴わない 46, XY DSD で新規 SF-1 遺伝子異常を認めた症例を経験したので報告する。

1．症　例

【症　例】日齢 6、新生児
【主　訴】外性器異常
【家族歴】特記すべきことなし
【現病歴】在胎 40 週 5 日 4276g にて出生。出生時外陰部は一見女性型であり、一度女児と診断されたが、両側大陰唇部に性腺と思われる 0.5ml の腫瘤を触知し、性判定の目的で日齢 6 に当院へ紹介となった。まだ出生届けは提出していなかった。
【身体所見】身長 53.8cm、体重 3945g。胸腹部に異常所見なし。皮膚色素沈着なし。外性器の状態は、女児としてみると軽度陰核肥大あり、陰唇癒合を認めた。尿生殖洞の開口部を陰核内に認め、膣口は認めなかった(図 1)。

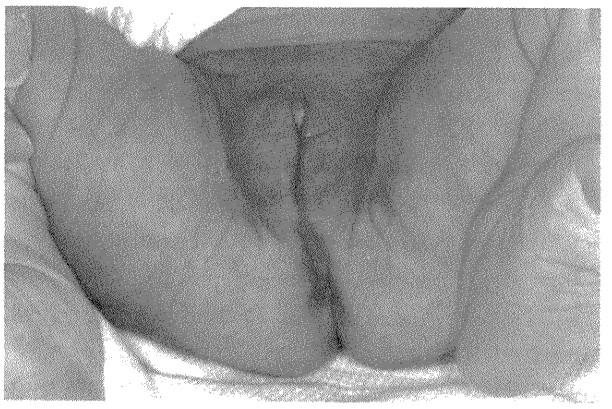


図 1：初診時外性器の状態

【検査所見】表 1 に示すように、血算に異常はなく、血液生化学検査では電解質異常、低血糖を認めなかった。内分泌学的検査所見では、LH-RH 負荷試験では LH の基礎値 0.20mIU/ml、頂値 1.91mIU/ml、FSH の基礎値 4.44mIU/ml、頂値 11.70mIU/ml と正常反応であった。hCG 負荷試験では、testosterone は前値、頂値ともに 0.05ng/ml 未満と無反応であった。ACTH 負荷試験で cortisol は基礎値 9.3μg/dl、頂値 37.1μg/dl (60 分後)と副腎機能は正常であった。また ACTH 38.3pg/ml、estradiol 15pg/ml であった。

染色体は 46, XY と正常男性核型であった。

表 1：検査所見

【血算】

RBC	408 × 104/mm3
WBC	12200/mm3
Plt	27.0 × 104/mm3

【血液生化学検査】

Na	143mEq/l
K	4.5mEq/l
Cl	106mEq/l
Cre	0.29mg/dl
Glu	84mg/dl

【内分泌学的検査所見】
[LH-RH 負荷試験]
LH 0.20 → 1.91 mIU/ml, FSH 4.44 → 11.70 mIU/ml
[hCG 負荷試験]
testosterone　前値、頂値ともに 0.05ng/ml 未満と無反応
[ACTH　負荷試験]
cortisol 9.3 → 37.1 (60 分後) μg/dl
[その他] ACTH 38.3pg/ml, estradiol 15pg/ml

【染色体核型】46, XY

【骨盤部 MRI(図 2)】子宮および両側卵巣は同定できず、両側陰嚢頭側部に精巣様構造を認めた。
【遺残尿生殖洞の内視鏡的逆行造影(図 3)】尿道括約筋より高位に 13mm の膣(男性膣)が確認された。
【精巣生検】日齢 16 に性腺生検を施行したところ、両側とも精巣様で未熟な精巣上体様付属器が存在していた。右性腺は 6×4×3mm、左性腺は 7×4×2mm と低形成であった。性腺病理の結果は精巣低形成(精細管のみよりなり、間質はやや広め、精細管内には胚細胞が認められるが数は減少傾向)であった。卵巣由来組織は認めなかった(図 4)。

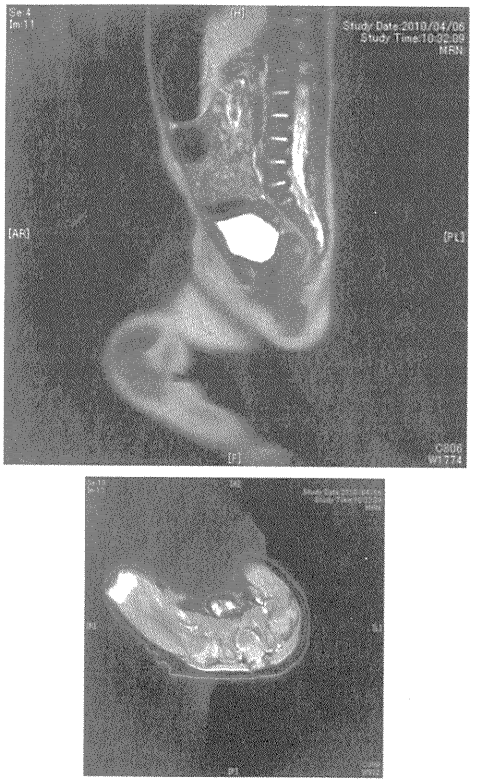


図 2：骨盤部 MRI
・子宮および両側卵巣は同定できず(上図)
・両側陰嚢頭側部に精巣様構造を認める(下図)

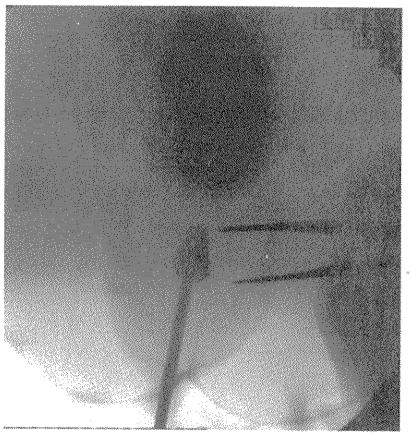


図 3：遺残尿生殖洞の内視鏡的逆行造影
尿道括約筋より高位に 13mm の膣(男性膣)を確認(ピンセットではさんだ部分)。

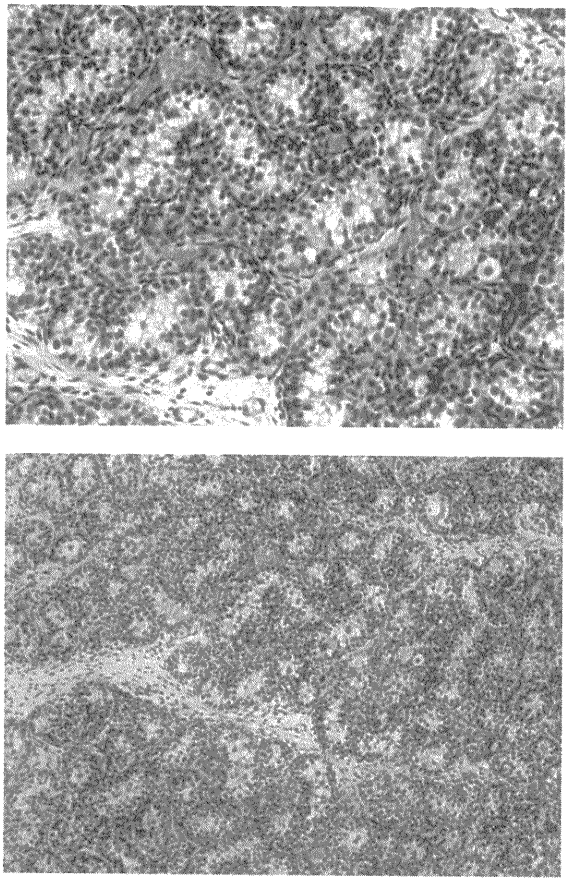
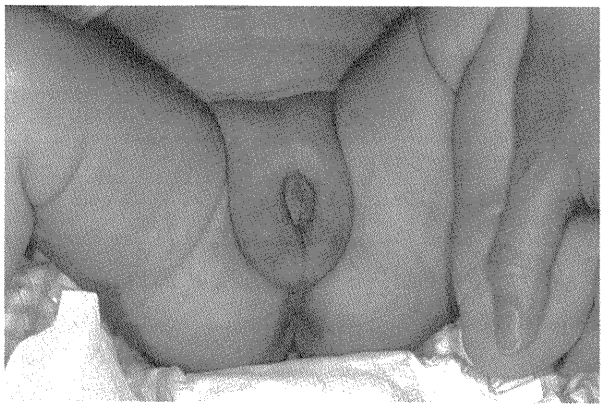


図 4：性腺組織(HE 染色)
精巣低形成(精細管のみよりなり、間質はやや広め(上図)、精細管内には胚細胞が認められるが数は減少傾向(下図))

【社会的性の決定】以上の結果を総合的に判断し、日齢 20 に児の性別を男児と決定した。男児とした理由としては、①染色体 46, XY と正常男性核型であったこと、②現在性腺よりの testosterone 分泌能はないものの精巣に分化しており、卵巣成分を認めないこと(患児血中 estradiol 15pg/ml は母体由来と考えられた[7])、③ミューラー管は消退し女性内性器を認めなかったこと、④女性にした場合の膣形成の困難さ(思春期過ぎた時点で代用膣による膣形成が必要となる可能性が高い)、⑤testosterone 投与にて陰茎の発育を期待できる、⑥精巣上体様附属器が存在していることを考えると胎生期 testosterone の暴露は少なからず存在したと考えられること、つまり脳の性分化に関しても将来男児として性の揺らぎが生じる可能性が少ないと考えられることである。
【治療経過】性別を男児と決定後、日齢 21 より testosterone 筋注による治療を開始した。エナルモンデポー®25mg を 3 週間毎に 12 回行い、陰茎の発育を認めた(図 5)。エナルモンデポー®25mg 筋注 1 週後の testosterone 値は 3.44ng/ml、3 週後は 0.25ng/ml であった。9 ヶ月までの成長曲線を図 6 に示す。

生後 3 ヶ月半(4 回投与後)



生後 8 ヵ月半(12 回投与後)

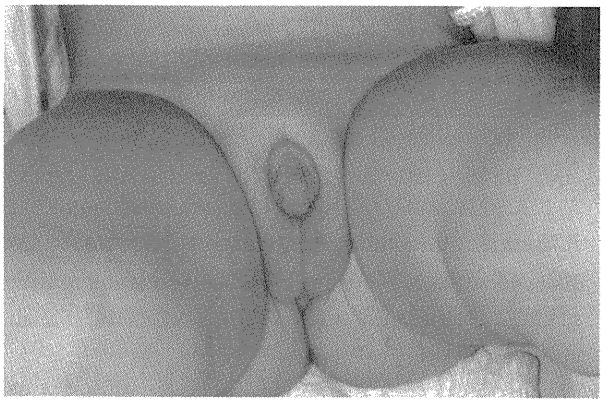


図 5：テストステロン投与後の外性器の変化(エナルモンデポー 25mg 筋注、3 週毎、12 回)

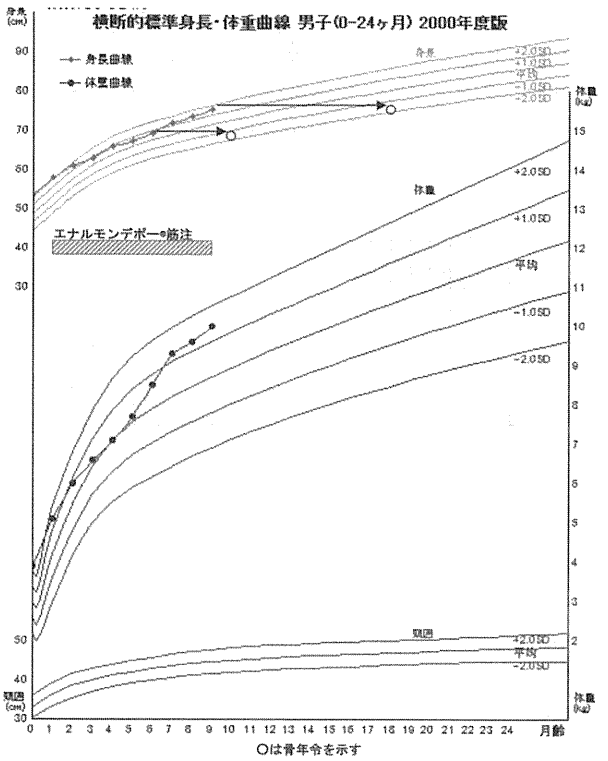


図 6：成長曲線

2．性分化異常をおこした原因の検索

一見女性用の外性器であったものの、染色体は 46, XY と正常男児核型であり、46, XY DSD であった。泌尿器系の異常はなく、副腎機能は正常であった。また性腺は低形成であるものの精巣に分化していたが、testosterone の分泌は hCG 負荷試験で無反応であった。以上より、今回性分化異常をきたした原因として Leydig 細胞低形成、SF-1 異常症を疑い遺伝子検索を行った。Leydig 細胞低形成の原因である hCG/LH 受容体遺伝子コード領域に異常は認めなかったが、SF-1 遺伝子の第 2 エクソンのコドン 83 でバリンがメチオニンに置換される pV83M ミスセンス変異がヘテロ接合体で同定された。両親に同変異は認めず de novo の変異であった(図 7)。pV83M 変異はこれまでに報告されていない変異であるため、CYP11A1 プロモーターを用いて機能解析を施行したところ、予想に反して V83M 変異体で、野生型よりも高い転写活性能を示した(図 8)。現在ターゲット配列の変更、細胞の変更を行い再解析中である。

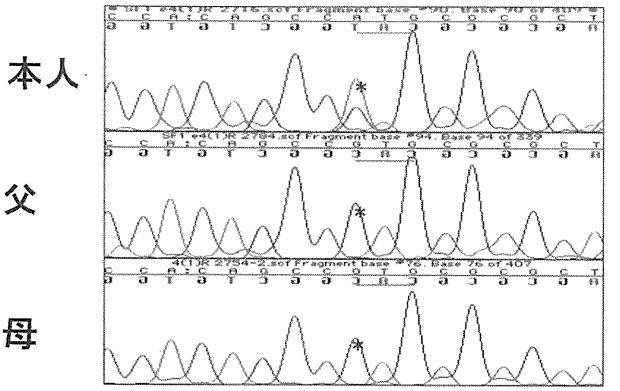


図 7：SF-1 遺伝子解析の結果
第 2 エクソンのコドン 83 でバリンがメチオニンに置換される pV83M ミスセンス変異がヘテロ接合体で同定された

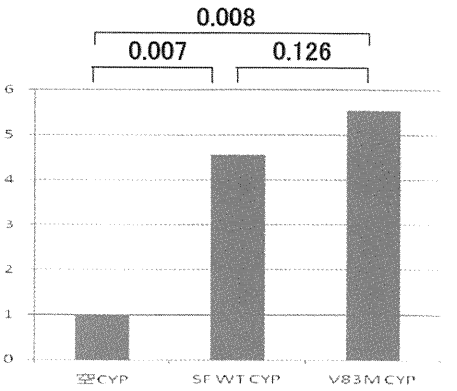


図 8：pV83M 変異の機能解析の結果(CYP11A1 プロモーター使用)
V83M 変異体で、野生型よりも高い転写活性能を示した

3．考　察

性分化異常症で社会的性の決定を行う際には染色体の性、性腺の分化、内性器の状態、外性器の状態、脳の性分化などを総合的に判断し、決定していく必要がある[8]。また両親のサポートも重要な課題であり、両親がその決定に迷うことなく育児をしていけるようサポートすることも重要である。今回我々の症例は、小児泌尿器科医の協力のもと、比較的速やかに性決定まで持っていくことができた症例と考えるが、実際に社会的性を決定するまでには両親を含めた話し合いを何度も持ち、最終的には両親も納得のいく形での社会的性の決定であった。はじめご両親は外性器の状態が女性型にかなり近かったため、陰茎の発育に関して不安を持っていたが、治療がすすむにつれ不安は消失した。

性分化異常をきたした原因として、Leydig 細胞低形成、SF-1 異常症を疑い遺伝子検索を施行した。Leydig 細胞低形成の原因である hCG/LH 受容体遺伝子コード領域に異常は認めなかったが、SF-1 遺伝子の第 2 エクソンのコドン 83 でバリンがメチオニンに置換されるという新規 pV83M ミスセンス変異がヘテロ接合体で同定された。SF-1 は副腎および性腺の発生、分化に必須な核受容体転写因子で、ヒトでは 1999 年に SF-1 の半量不全による 46, XY DSD と副腎不全を発症した症例がはじめて報告されたが[1]、その後は 46, XY DSD の症例では副腎不全を伴わないものが多く報告されている[3)-6)]。既報の SF-1 遺伝子異常の一部を図 9 に示す[9]。本症例も SF-1 異常症に症状は合致すると考えたが、pV83M 変異は新規変異であるため、CYP11A1 プロモーターを用いて機能解析を施行した。結果は、転写活性能は低いであろうという予想に反して V83M 変異体で、野生型よりも高い転写活性能を示した。現在ターゲット配列の変更、細胞の変更を行い再解析中であるが、この新規変異が病因となっているかは更なる検索が必要であり、本症例の DSD の原因に関しては、まだ未解明な部分がある。

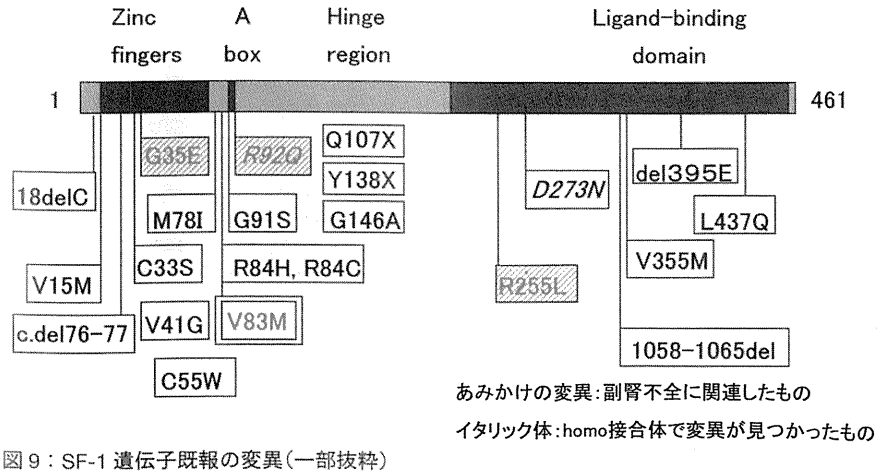


図 9：SF-1 遺伝子既報の変異（一部抜粋）
□：本症例の変異

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《特集Ⅰ》第29回日本思春期学会総会学術集会

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男性性器異常患児における思春期の問題点

北海道大学大学院医学研究科　腎泌尿器外科学分野

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野々村克也

性分化異常症においては，出生直後の養育すべき社会的性の決定（gender assignment）とともに，決定した性に従った外陰形成術（genitoplasty）が必要である。男性性器異常患児では外陰形成術として尿道下裂形成術・精巣固定術・陰嚢形成術などが行われ，その目標とするところは女子外陰形成術も含め，1）決定された性に一致した外陰の外観の確保，2）尿失禁や尿路感染を伴わない正常な排尿機能の確保，3）成人に達した時の性機能・生殖機能の確保にある[1]。このような形成術は患児の生命維持に直接結び付かないことから，1960年代には学童期に入る前までに行うことが基準となっていた。その後1980年代には，小児に対する麻酔の発達や拡大鏡下のマイクロサージャリー技術の導入を背景に，患児の精神発達の観点より2歳を目処として形成術が行われるようになった。医療技術・環境の進歩につれ，形成術の早期施行が進む一方で，本人の意思確認をしない段階での不用意な手術と患者団体からの批判も登場してきた[2]。しかし，これら乳幼児期に行われた外陰形成術の長期成績に関する国内外の報告は少なく，適切な手術時期・術式に関してのエビデンスが求められている。今回，尿道下裂の手術を受けた患児が思春期に達した時の性機能，精神心理的問題に関しての調査結果を述べる。

尿道下裂は，男性への性分化異常の一徴候としてみられ，停留精巣に次いで多い外性器異常である。その状態を放置することにより外観の異常は勿論，患児の男性としての精神心理的発達にも影響を及ぼすことが懸念され，高度の下裂にあっては立位排尿や性行為が困難となる（図1）。したがって，尿道下裂形成術は外陰の正常な外観を得ると同時に，陰茎の屈曲を矯正し，外尿道口を陰茎先端に形成することを目的として，患児に性の

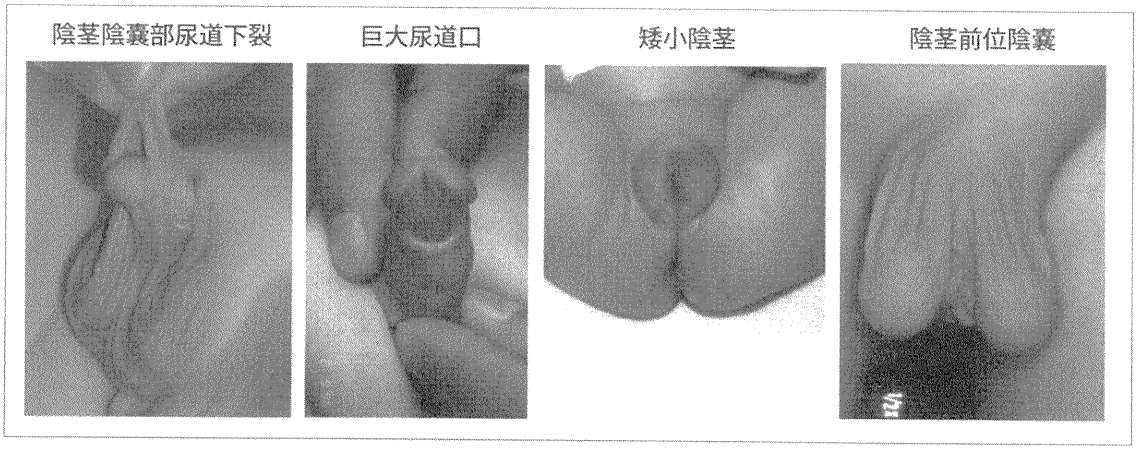

図1 尿道下裂の形態・種類

認識が芽生える以前に行われてきた。現在行われている術式において，その外観や立位排尿に関する短期成績に関して良好であるとする報告は枚挙に暇がない。一方，長期成績についての国内外の報告はわずかにすぎない。われわれが1980年代に尿道下裂形成術を行った患児の排尿・性機能についての長期成績を紹介する[3)4)]。

方　法

1983年以降に6歳以下で初回手術を受け，18歳以上に達した症例で接触可能な33例を下裂症例群とし，外陰の手術既往のない18歳以上の男性50例を対照群と比較検討した。

両群に自己記入式質問表に記入のうえ，郵送にて回収した。質問紙が返却された22例（遠位型9例，近位型11例，不明3例）について，38例の対照群と比較した。22例中16例はわれわれが開発した外尿道口周囲の包皮を尿道形成に用いる一期的尿道下裂形成術が行われている[5)]。1) 排尿症状に関する検討質問内容は①尿線の方向，②尿勢，③頻尿，④排尿姿勢，⑤尿の切れの五項目とした。2) 性機能に関する検討では陰茎の外観として，①大きさ，②瘢痕，③包茎，④屈曲，⑤外尿道口の位置，⑥全体の形，⑦亀頭の形などの項目について質問のうえ，①勃起能，②性欲，③勃起時陰茎の屈曲，④勃起時の問題の性行動に関する4項目を設定した。また，性行動の指標として，①自慰/性行為の初経験年齢，②射精/性交時についても問題とした。

結　果

1）排尿に関し，①尿線の方向，②尿勢，③頻尿，④排尿姿勢については下裂例と対照例に有意な差異はみられず，大多数例で排尿に支障がないと判断される（図2）。唯一，高度尿道下裂例で尿の切れが悪く，下着の汚れを防ぐために排尿後に尿道をしごくなどの操作を必要としていた（図3）。高度尿道下裂では形成新尿道が長く，通常尿道を包んでいる尿道海綿体や球海綿体筋の欠損などが関与していると考えられる。

2）性機能／性行動に関しては，外観上の問題点や満足度は全体として両群に差はみられなかっ

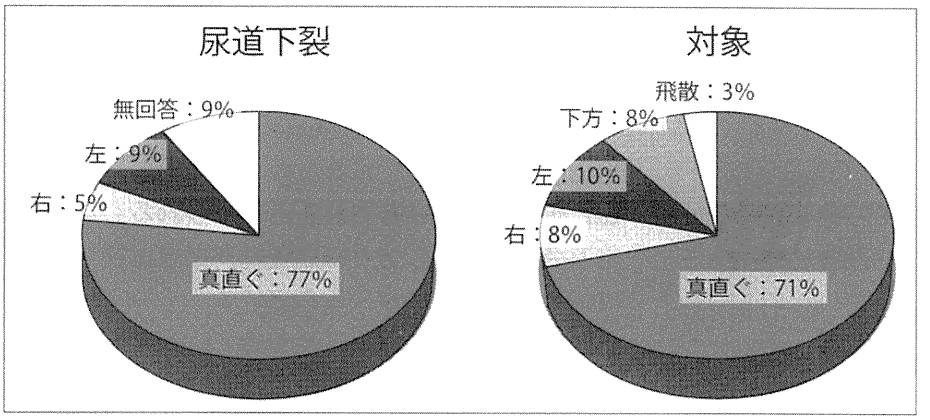

図2　尿道下裂形成術後長期観察
排尿状態

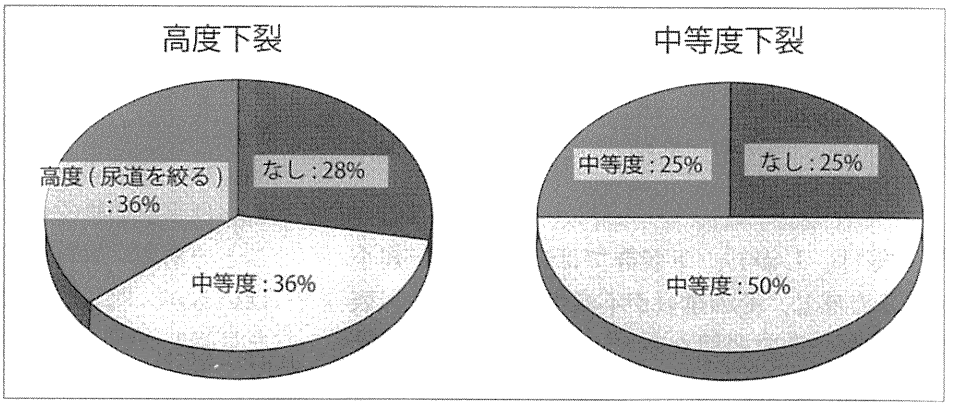

図3　尿道下裂形成術後長期観察
下裂の程度による排尿後の尿の切れ