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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consensus statement on the management of intersex disorders was published in 2006.[1] The term "true hermaphrodite" has been replaced by ovotesticular disorder of sex development (DSD), defined as the presence in the same individual of ovarian tissue containing ovarian follicles and testicular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.

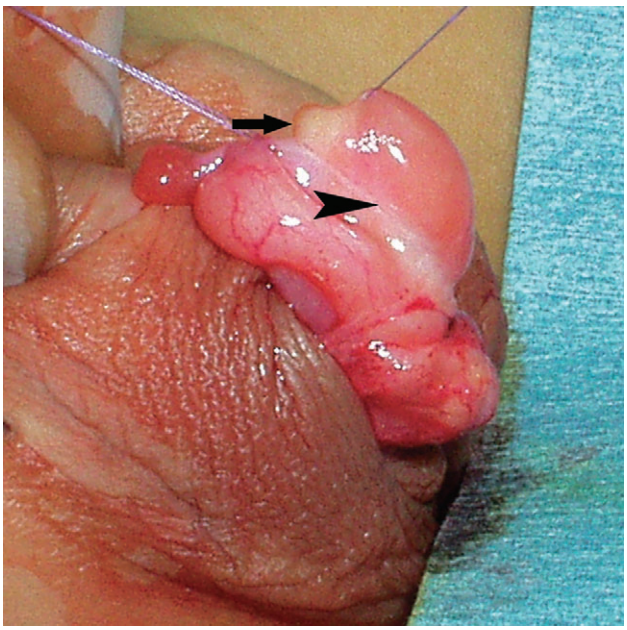

Fig. 1 Macroscopic findings of ovotestis. Ovarian portion (arrow) is firm and yellow in an upper pole, whereas testicular portion (arrowhead) is soft and pink in a lower pole. There is a distinct line of demarcation between the two portions.

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

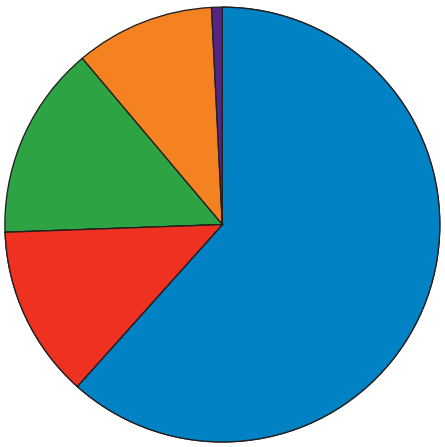

Fig. 2 Chromosomal distribution of 125 patients with ovotesticular DSD published in the literature in Japan. ■, 46,XX (77 patients, 61.6%); ■, 46,XY (16 patients, 12.8%); ■, 46,XX/XY (18 patients, 14.4%); ■, other mosaicism (13 patients, 10.4%); ■, other (1 patient, 0.8%).

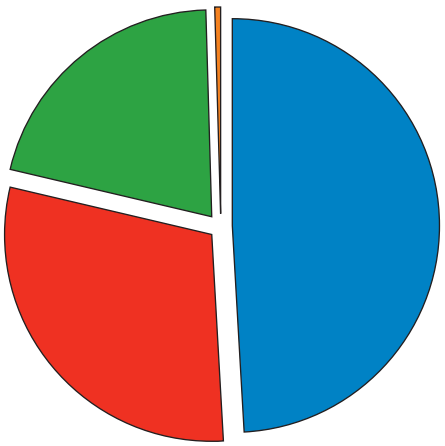

Fig. 3 Gonadal distribution of 324 gonads of a total of 165 patients with ovotesticular DSD published in the literature in Japan. ■, ovotestis (159 gonads, 49.1%); ■, ovary (96 gonads, 29.6%); ■, testis (67 gonads, 20.7%); ■, streak (2 gonads, 0.6%).

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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