The Long-Term Followup of 33 Cases of True Hermaphroditism: A 40-Year Experience With Conservative Gonadal Surgery

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Purpose: Little is known about long-term outcomes of conservative gonadal surgery in true hermaphroditism. We present our experience with evaluation and treatment of a large series of children with this rare form of ambiguous genitalia, focusing on gonadal structure and function before and after conservative gonadal surgery.

Materials and Methods: We retrospectively reviewed 33 consecutive patients with histologically confirmed true hermaphroditism treated at the Hopital des Enfants-Malades between 1965 and 2005.

Results: The most common karyotype of true hermaphrodites was 46,XX, constituting 82% of our series. The frequency of finding the *SRY* gene in 46,XX cases was 35%. Ovotestis was the most frequent finding (65%) and testis the rarest (9%). Ovarian tissue was more often found on the left side, and testicular tissue on the right side ($p < 0.05$). Proper gonadal tissue was preserved in 28 cases. No gonadal tumors were detected during followup. Ovarian tissue remained normal, while testicular tissue gradually developed signs of dysgenesis in all biopsied cases, confirmed by endocrinological studies. However, testosterone production remained satisfactory in the majority of cases during followup.

Conclusions: Diagnosis of true hermaphroditism is well defined and the condition can be recognized even prenatally. Conservative gonadal surgery is the procedure of choice after a diagnosis of true hermaphroditism. Continued followup is necessary because of the multiple psychological, gynecological and urological problems encountered postpubertally by these patients.

Key Words: sex differentiation disorders, hermaphroditism, gonads, genitalia

True hermaphroditism is defined as the presence of testicular and ovarian tissue in the same individual. In infancy the gonads appear to have normal ovarian tissue with numerous follicles and normal testicular tissue with seminiferous tubules containing germ cells. As time passes, the ovarian tissue usually remains functional and the testicular tissue becomes abnormal, with incomplete development, loss of germ cells and tubular sclerosis.

We had the opportunity to evaluate and treat a large series of children with this rare form of ambiguous genitalia. We retrospectively reviewed the data on these 33 children with histologically confirmed TH treated at the Hopital des Enfants-Malades between 1965 and 2005. This review focused on gonadal structure and function before and after conservative gonadal surgery.

MATERIALS AND METHODS

The study group comprised children from Europe, Africa and the Antilles. Five children had a prenatal diagnosis of ambiguous genitalia found on routine prenatal ultrasound. In 2 patients the diagnosis of TH was further verified prenatally by amniocentesis and determination of karyotype, presence of *SRY* gene, concentrations of testosterone and precursors of cortisol. A total of 28 patients presented with ambiguous genitalia from birth to age 8 years, with most (73%) presenting before age 6 months.

Standard karyotyping was performed on peripheral blood leukocytes in all cases, on fibroblasts in 5 cases and on gonadal tissue in 8 cases. *SRY* gene was studied by fluorescence in situ hybridization in 13 patients and polymerase chain reaction in 4.

Leydig cell function was evaluated before surgery by measuring plasma testosterone concentration (normal laboratory values for men 3.5 to 8.5 ng/ml, women 0.18 to 0.50 ng/ml; upper control value in female infants 0.15 ng/ml) before and after stimulation with HCG.[1] Data were available in 25 patients. A total of 18 patients received three 1,500 IU HCG injections every other day, and 7 received 5 to 7 injections every other day. Sertoli cell function was evaluated by measuring plasma AMH concentration in the last 12 patients (preoperatively in 10). All measurements were performed by radioimmunoassay.

The type of gonadal surgery remained the same during the study period.[2] Conservative gonadal surgery is the procedure of choice, meaning partial resection of ovotestes guided by intraoperative histological examination with maximum preservation of tissue concordant with sex of rearing,

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TABLE 1. *Gonadal distribution in 33 cases.*

1 Side	Contralat Side	Total No.
Ovary	Testis	3
Ovotestis	Ovary	14
Ovotestis	Testis	3
Ovotestis	Ovotestis	13

and resection of all discordant tissue. We calculated the percentage of testicular tissue in each gonad and in each individual. The presence of a vas deferens and/or fallopian tube was evaluated at surgery and histological examination of resected specimens. The technique of genitoplasty has been described previously and was subject to significant change during the study period.[3] Clitoral plication was used before 1980 and was replaced with cavernous resection thereafter. Vaginoplasty was always feasible through the perineal approach. If masculinizing genitoplasty was performed, 1-stage hypospadias repair replaced the 2-stage repair used in the early period of the study.

Data were analyzed with the SAS® 8.2 statistical package. Results of continuous variables are presented as the median (range). The association between categorical variables was tested using chi-square analysis, and the association between continuous variables was analyzed with the Mann-Whitney test. A p value ≤ 0.05 was considered statistically significant.

RESULTS

The position and distribution of the gonads in all patients are summarized in tables 1 to 3. Ovotestis was the most frequent finding (65%) and testis the rarest (9%). Ovarian tissue was more often found on the left side, and testicular tissue on the right side ($p < 0.05$). Right ovotestes were situated lower than left ovotestes ($p < 0.001$). In 1 case left-to-right crossed ectopia of an ovotestis was diagnosed.

Proportions of both tissues were described in 16 cases of right ovotestis and 12 cases of left ovotestis (fig. 1). On the right side median percentage of testicular tissue was 90% in scrotal and 66% in undescended gonads ($p < 0.05$). Ovarian and testicular tissue was usually arranged in an end-to-end fashion (88% of cases), with distinct separation in most cases. The ovarian portion was represented by a smaller triangular polar prolongation of the round testicular section in 50% of ovotestes (fig. 2). The tunica albuginea of the testicular part was fenestrated or absent and had a particular appearance on histological examination (figs. 2 and 3).

Microscopic examination of the testicular parenchyma showed normal seminiferous tubules with germ cells in all 5 patients evaluated during the first month of life. Germ cells were present in 67% of testicular biopsies in the first year of life, in 37% from age 1 to 8 years and in only 1 of 5 evaluated at pubertal and postpubertal ages. In no case was spermatogenesis noted. On the contrary, examination of ovarian tissue revealed numerous follicles in all cases (fig. 4). Ovulatory changes were observed postpubertally.

TABLE 2. *Side of gonad*

Gonad	No. Lt	No. Rt	Total No.
Ovary	12	5	17
Testis	2	4	6
Ovotestis	19	24	43

TABLE 3. *Position of gonad*

Gonad	No. Abdominal	No. Inguinal	No. Scrotal	Total No.
Rt ovary:	4	1*	0	5
Testis	0	2	2	4
Ovotestis	5	10	9	24
Lt ovary:	12	0	0	12
Testis	0	0	2	2
Ovotestis	10	6	3	19

* Situated in a patent hernial sac.

A uterus was present in 73% of cases (hemiuterus in 48% and normal uterus in 25%). When the uterus was normal the median proportion of testicular tissue in both gonads was 38%. When a hemiuterus was present the proportion was 51%, and when no uterus was found it was 71% ($p < 0.05$). The hemiuterus was on the side with less testicular tissue.

All 6 testicles had an epididymis and a vas deferens. In 2 cases a remnant of the infundibulum of a tube was also present. One of 17 ovaries had a remnant of epididymis closely attached to the tube. Ovotestes from both sides had variable adnexa. Mullerian and wolffian derivates were present in 24% of cases on the right and 58% on the left side ($p < 0.05$, fig. 5).

The most common karyotype obtained on blood sample was 46,XX (27 patients, 82%). Cytogenetic analyses demonstrated a 46,XX/46,XY karyotype in 4 patients and a 46,XX/47,XXY in 2. A total of 17 children with karyotype 46,XX underwent complementary studies. Of these patients 6 (35%) had the *SRY* gene. Two cell populations, 46,XX and 46,XY, were found on fibroblasts or on gonads in 2 patients. In 1 familial case a segment of Yp containing *SRY* was translocated onto distal Xp by crossover outside the pseudoautosomal region during meiosis.

There were 2 familial cases. One patient previously studied had a 46,XX sibling with bilateral dysgenetic testicles.[2] The other case involved 46,XX twins diagnosed at birth, 1 with an ovotestis and an ovary, and 1 that was more virilized with bilateral ovotestes.

A total of 21 patients were reared as female and 12 as male. Six infants were treated before declaration of sex, 5 as female and 1 as male. Only in 5 earlier cases was bilateral castration carried out. Resection of inappropriate gonadal

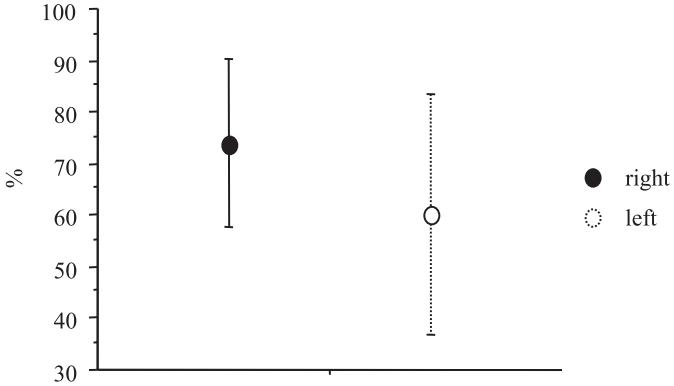

FIG. 1. Percentage of testicular tissue present in 28 ovotestes (right vs left side, $p = 0.08$).