ISOLATED CLITORAL ENLARGEMENT DUE TO TRUE HERMAPHRODITISM

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SUMMARY – True hermaphroditism represents a heterogeneous condition in terms of its phenotypic presentation and genetic background. There is a wide spectrum ranging from frankly male to frankly female external genitalia, however, with a predominance of ambiguity. The most frequently observed karyotype is 46,XX, followed by various types of chromosome mosaicism, whereas the rarest one is 46,XY. Simultaneous presence of testicular and ovarian tissue either in separate gonads or in one named ovotestis is required for the diagnosis. In neonatal period our patient was noted to have isolated clitorimegaly (15 mm) with otherwise normal female external genitalia and no palpable gonads either in labia or in inguinal areas. The levels of electrolytes, 17-hydroxyprogesterone (17 OH P), androstenedione and renin were within the reference values. Baseline plasma level of testosterone was elevated as well as its response in the human chorionic gonadotropin (hCG) stimulation test. The presence of uterus was discovered by imaging techniques but gonadal localization was not possible. Karyotype was 46,XY. According to clinical and laboratory findings, the diagnosis of 46,XY partial gonadal dysgenesis was made. During surgery, reduction of clitoris was performed while laparotomy revealed a right ovotestis (confirmed by histology) which was removed. The left gonad was not identified and biopsy of suspected tissue revealed fallopian tube. Considering obvious female appearance of external genitalia and its potential function, it was suggested that the baby should be reared as a girl. As there is no clinical, laboratory or imaging finding which could differ true hermaphroditism from some other types of intersex, definitive diagnosis depends on gonadal histology.

Key words: Hermaphroditism – diagnosis; Hermaphroditism – surgery; Gonadal dysgenesis; Gender identity; Karyotyping; Sex differentiation disorders – surgery; Case report

Introduction

True hermaphroditism is a heterogeneous condition in terms of its phenotypic presentation and genetic background. There is a wide spectrum ranging from frankly male to frankly female external genitalia, however, with a predominance of ambiguity. The most frequently observed karyotype is 46,XX, followed by various types of chromosome mosaicism, whereas the rarest one is 46,XY. Simultaneous presence of testicular and ovarian tissue either in separate gonads or in one named ovotestis is required for the diagnosis1,2.

Case Report

The baby was born after the 2nd uncomplicated pregnancy. There was no history of maternal drug ingestion. At the time the patient was born, the parents were young and healthy, mother aged 23 and father aged 26. Sister aged 2 years was also healthy. Family history included no data on unexplained childhood deaths. Maternal grandmother had hypothyroidism and dyslipidemia, and grandfather had diabetes mellitus type 2.

The patient was born at 38 weeks of gestation by natural, uncomplicated delivery. Birth weight was 3940 g, length 52 cm, Apgar score 10/10. Phototherapy was administered for hyperbilirubinemia.

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At birth, the baby was noted to have hypertrophic clitoris (15 mm), with otherwise normal female external genitalia consisting of labia, normally situated urethral meatus and a separate vagina. The gonads were not palpable either in labia or in inguinal areas.

On day 10 of life, laboratory studies revealed normal serum electrolyte levels with 17-hydroxyprogesterone (17 OH P) 29 nmol/L, androstenedione 3.3 nmol/L, dehydroepiandrosterone sulfate (DHEAS) 1.04 mmol/L. The level of testosterone was 1.1 nmol/L (elevated for a female baby). The levels of cortisol, corticotropin (ACTH), aldosterone and renin were within the normal limits. Luteinizing hormone (LH) was 3.4 IU/L, follicle-stimulating hormone (FSH) 18.7 IU/L, and estradiol was undetectable. Chromosome analysis on peripheral blood showed the 46,XY karyotype.

At 3 weeks of age, 17 OH P was 21 nmol/L and androstenedione 3.4 nmol/L. Baseline level of T was 3.0 nmol/L and its level in hCG test after 1000 IU of human chorionic gonadotropin for 3 days was 7.3 nmol/L, which pointed to the presence of active Leydig cells. Pelvic ultrasound examination identified neither uterus nor gonads. A genitogram demonstrated the existence of vagina with a cervical imprint (Fig. 1). Radiography revealed vesicoureteric reflux (VUR) grade II, with no signs of possible fistula between the urethra and vagina.

According to physical and laboratory findings, the diagnosis of 46,XY partial gonadal dysgenesis was made. It was planned to perform clitoral reduction and extirpation of the dysgenetic gonads because of the known high prevalence of gonadal tumors. Prophylaxis of urinary tract infection was suggested due to grade II VUR.

The female gender was assigned on the basis of the female appearance of external genitalia and their potential function.

On outpatient control visit at the age of 4 months, the patient’s length was 66.5 cm (3.8 SDS), weight 6.2 kg, and physical examination was normal except for the clitoral enlargement. The level of 17 OH P was 6.0 nmol/L and of testosterone <0.5 nmol/L, both within the

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**Fig. 1. A genitogram demonstrating the existence of vagina with a cervical imprint.**

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**Fig. 2a and 2b. Testicular tissue with partially calcified tubules (2a) and normal ovarian tissue with follicles (2b).**
normal reference values. At 2 years of age while the child was preoperatively hospitalized, bCG test was performed again and testosterone levels of 0.5 basally and 4.3 nmol/L on day 3 suggested the presence of functional testicular tissue. At that time the patient’s height was 92.5 cm (2.3 SDS) and weight 14 kg. Surgery was performed aiming at identification and extirpation of gonads and correction of clitoris. Clitoral reduction with preservation of the dorsal neurovascular bundle and clitoral glans was done. Laparotomy revealed a right gonad, which was removed entirely. Histology showed an ovotestis consisting of normal ovarian tissue with follicles and testicular tissue with partially calcified tubules associated with normal epithelium (Fig. 2a,b). On that side neither fallopian tube nor vas was detected. The left gonad was not detected and presumed tissue biopsy revealed a fallopian tube. Based on histology, a definitive diagnosis of true hermaphroditism was made.

Currently, the girl is 5 years old; her height is 114.5 cm (1.4 SDS), weight 19.5 kg, WFIH 94%, and BMI 15.1 kg/m². Pubarche and pubarche are grade I according to Tanner. Control hCG test with testosterone levels on day 1 and 3 below 0.5 nmol/L excludes the activity of Leydig cells. The gonads are not visualized by pelvic ultrasound and the uterus appears like a fibrous streak.

Discussion

True hermaphroditism is a rare cause of ambiguous genitalia, and its main characteristic is the simultaneous presence of testicular and ovarian tissue, either in the same or in opposite gonads. The degree of virilization of external genitalia and the presence of both müllerian and wolffian structures are influenced by the number of functional testicular tissue.

In true hermaphroditism the ovarian tissue is usually functional. On the contrary, the testis or testicular tissue from ovotestis is often compromised regarding hormonal function as well as spermatogenesis. The level of masculinization depends on the number of functionally active Leydig cells, and development of structures originating from müllerian ducts upon the number of functional Sertoli cells.

In our child, according to clinical presentation which included mild virilization of external genitalia, presence of uterus, male karyotype and active testicular tissue, at first the possibility of gonadal dysgenesis (GD) was considered. Differential diagnosis included true hermaphroditism as well as congenital adrenal hyperplasia (CAH), androgen insensitivity syndrome (AIS), enzyme defects of testosterone biosynthesis, and Leydig cell hypoplasia.

46,XY gonadal dysgenesis comprises complete and partial form. Complete gonadal dysgenesis (CGD) in individuals with 46,XY karyotype is characterized by female phenotype including totally nonambiguous female genitalia, normally developed structures originating from müllerian ducts, and streak gonads. Delayed puberty is a frequent clinical presentation. On the contrary, in 46,XY partial gonadal dysgenesis (PGD) testicular differentiation is incomplete with the disturbance affecting the function of both Leydig and Sertoli cells. Inadequate secretion of testosterone and müllerian inhibiting substance (MIS) results in ambiguous, incompletely differentiated genitalia and incomplete suppression of müllerian duct formation. Individuals affected by this syndrome have fully or partially formed uterus, and a low level of androgens in the neonatal period. According to clinical presentation, laboratory and imaging findings, without gonadal histology, in our child this diagnosis seemed most likely.

In spite of the initially elevated level of 17 OH P, its fall, the karyotype and other findings did not point to the diagnosis of CAH.

In individuals with the complete androgen insensitivity syndrome (CAIS), the levels of testosterone are normal or high while gonadotropins (LH, FSH) are usually elevated. This diagnosis also includes the presence of testes, spontaneous breast development at puberty, primary amenorrhea, and absent or sparse axillary and pubic hair. Identification of an androgen receptor gene mutation definitely confirms the condition. In the partial androgen insensitivity syndrome (PAIS), androgen production is normal or mildly elevated; there is a shallow vagina without uterus. The gold standard for the diagnosis of PAIS is demonstration of an androgen receptor gene mutation. Those patients should be differentiated from patients with 17β-hydroxysteroid dehydrogenase-3 (17β-HSD-3) deficiency, where estrone is produced from androstenedione without testosterone.

Steroidogenic enzyme defect, which results in inability to produce testosterone or dihydrotestosterone, can also be the etiologic basis. This diagnosis requires evaluation of testosterone, dihydrotestosterone and all
the precursors (pregnenolone, 17 OH pregnenolone, dehydroepiandrosterone, 17 OH progesterone and androsterone). The lack of the end product with accumulation of precursors indicates a specific biosynthetic abnormality due to the underlying gene mutation, which can be confirmed by time-consuming and expensive mutation studies.

Another possibility includes Leydig cell hypoplasia which leads to decreased androgen secretion and partial virilization of genitalia. In some patients this is the possible consequence of LH receptor mutations. It can be expected that the function of Sertoli cells is normal as well as the level of MIS; however, in some patients this is not the case, namely, they present with signs of MIS deficiency similar to PGD4.

In true hermaphroditism the most common gonadal combination is ovotestis and ovary, followed by bilateral ovotestis. Ovaries are more common on the left side (left 76.5%, right 23.5%), whereas gonads containing testicular tissue are usually found on the right side (right 60.3%, left 39.7%)2,6. The existence of ovarian tissue cannot be proved preoperatively because of the absence of a reliable functional test. Mendes et al. have reported on hMG (human menopausal gonadotropin) stimulation test results in 11 children with ambiguous genitalia and four control male subjects. They used 2 IU/kg hMG i.m. every 12 hours for 7 days. If after the level of estradiol (E2) was below 80 pg/mL, the test was prolonged with a double dose of hMG for additional 7 days unless more than 80 pg/mL E2 was detected. In five children the test was positive, which pointed to the existence of ovarian tissue, which was subsequently confirmed by histology. In two children who were assigned as male ovarian tissue was eliminated and retesting at 6 months showed no elevation of estrogen. The level of E2 80 pg/mL is arbitrary. Further studies in a larger number of patients are needed to confirm the specificity and sensitivity of this test.1 In our patient ovotestis was on the right side, whereas the other gonad could not be identified. Control hCG test excluded the existence of functional testicular tissue, so if the left gonad existed it could have been the ovary. However, control pelvic ultrasound performed at the age of 4 years did not show any gonads.

The localization of gonads may also be done by magnetic resonance imaging (MRI) of the pelvis, however, considering the age of the patient and the need of general anesthesia, this diagnostic procedure has not been performed to date. MRI is also advocated to differentiate between ovaries and testes, yet some authors report that both ovaries and testes have the same signal intensity on T-1 and T-2 weighted images. As the laboratory and/or imaging findings often have difficulties in localization and differentiation of gonads, laparotomy or laparoscopy are needed for visualization of internal genitalia, for gonadal biopsy or gonadectomy. Histologic analysis provides the information necessary for the diagnosis and helps us decide about the child’s gender. That is why laparoscopy or laparotomy are basic diagnostic tools, which should in case of doubts about the child’s gender be performed as early as possible. In our child the appearance and potential function of external and internal genitalia determined the female sex of rearing. In agreement with parents, the laparotomy aiming at localization and extirpation of the presumed dysgenetic gonads was postponed. Malignant gonadal transformation is reported in 2.6% to 4.6% of cases, mainly at age ranging from 14 months to 80 years. The most common malignant change occurs in ovotestis but it may grow from ovary or testis too.

The most frequent karyotype in true hermaphroditism is 46,XX (71%), followed by mosaicism (frequently 46,XX/46,XY in 20%), while the karyotype 46,XY, present in our child, is the rarest one (7%)3,6. A small percent of true hermaphrodites are chimeras, who have two distinct populations of cells (XY and XX cells), each of which have a different genetic origin (double fertilization or, possibly, fusion of two normally fertilized ova). On the contrary, in mosaicism two or more types of cells arise from mitotic or meiotic errors. Nowadays, the majority of cases of true hermaphroditism have no identifiable cause. The change from male to female phenotype in 46,XY individuals is a consequence of disturbed testis development, which can be caused by deletion or mutation in the SRY gene. SRY gene (sex determining region of the Y chromosome) starts the process of differentiation of male gender in mammals. SRY gene encodes a small, testis specific protein which contains HMG (high mobility group) box, located in many transcription factors, which stimulates and/or suppresses target genes that initiate masculine differentiation. SRY gene mutations are responsible for 10%-15% of 46,XY gonadal dysgenesis. Till today near 40 mutations have been discovered, most of which are located in HMG box domain. SRY gene mutations most often result in 46,XY female phenotype, without tests differentiation or complete gonadal dysgenesis. Some cases of true hermaphroditism and partial gonadal dysgenesis are also de-
scribed in connection with SRY gene mutations. In our child the presence of SRY gene on Y chromosome was proved in peripheral blood by fluorescence in situ hybridization (FISH) study, however, we have not been able to analyze for possible mutations till now.

The management of a child with ambiguous genitalia is complex and controversial. The child’s sex is assigned with respect to the underlying cause, assessment of the external and internal genitalia according to appearance and function, and potential psychosexual orientation. After that it was common to perform surgical procedure as early as possible, with the goals of extirpation of gonads and internal genitalia that oppose the sex of rearing and construction of “appropriate” external genitalia. However, recently many individuals and especially patient groups like Intersex Society of North America (ISNA) are opposing the idea of an early operation, labeling it as harmful, essentially cosmetic, and significantly increasing the risk of impaired sexual function in the future. Early surgical intervention seems reasonable only when there is a severe degree of hypopadidia, or if there is a high risk of infection associated with the presenting anomaly. In all other circumstances, surgery delay is advised until the patient can make his/her own informed decision, and parents should be included in deciding on the timing and extension of surgery. This approach should involve psychological support to the parents and later to the child, because it is not possible to determine the child’s sex during the initial few weeks after birth and thereafter. Without appropriate support, this situation may cause many problems for both the parents and the child, and may seriously disturb their relationship.

These problems arise from the fact that psychosexual orientation does not depend solely on the appearance of external genitalia because the central nervous system also plays an important role. The importance of the prenatal level of androgens is not yet completely known. More data are expected from studies of patients with congenital adrenal hyperplasia who are exposed to excessive androgens in the prenatal period, but the results of such studies are not without controversies. While some studies conclude that a significant number of female patients with CAH display male behavior and sexual orientation, others disagree with this opinion. Patients with true hermaphroditism are exposed to testosterone antenatally and they may also be exposed to a male physiological testosterone surge at approximately 2 months of age (dependent on the amount of function-
al testicular tissue). This may have repercussions on brain masculinization and could consequently be important for the timing of surgery and removal of testicular tissue in an infant with hermaphroditism assigned the female sex. As definite conclusions have not yet been made, the current practice is to remove sex inappropriate gonadal tissue in order to prevent the production of inappropriate hormones at puberty and because of the malignant potential of dysgenetic gonads.

It is widely accepted that adequate masculinization of the external genital requires adequate effects of androgens. Because of that, the degree of undermasculinization will be proportional to the degree of androgen deficiency regardless of its cause, implying either inappropriate production or insufficient response to androgens. Accordingly, it can be presumed that fetal brain is masculinized under the influence of androgens, but patients with inadequately virilized genitalia were exposed to androgen effects below the normal male range. Thus, regardless of whether this is crucial for later psychosexual development, the degree of decreased prenatal androgen exposure can be assessed by the appearance of external genitalia at birth. Because of that, whatever the cause of genital ambiguity in 46,XY patients, the most feminized patients would benefit from female sex of rearing and the most masculinized patients would optimally respond to male sex of rearing.

Conclusion

True hermaphroditism continues to be an intriguing disorder which poses significant diagnostic and management challenges. Despite advances that have been made in the understanding of the genes involved in sex determination, the underlying gene defects associated with true hermaphroditism are not known. As there is no specific clinical, laboratory or imaging finding by which true hermaphroditism could be differentiated from some other types of intersex, definitive diagnosis depends on gonadal histology. Therefore, early laparoscopy and/or laparotomy, especially in case of significantly undifferentiated genitalia, help establish an accurate diagnosis and decide on the patient’s gender and further therapeutic procedures.

References


Sažetak

IZOLIRANO POVEĆANJE KLITORISA ZBOG PRAVOG HERMAFRODITIZMA

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Ključne riječi: Hermafroditizam – dijagnostika; Hermafroditizam – kirurgija; Gonadna dijagnostika; Spolni identitet; Kariotipiziranje; Poremećaji spolne diferencijacije – kirurgija; Praktički slučaj

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