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Androgen Insensitivity Syndrome

Complete virilization of a 46XY fetus depends on either androgens or a functioning androgen receptor. Androgen insensitivity syndrome (AIS) is an X-linked recessive genetic condition caused by an androgen receptor gene mutation situated in the Xq11-q12 region, which results in resistance to androgens in 46XY individuals. The disorder is characterized by the presence of a male karyotype with a female phenotype. AIS is divided into subtypes that include complete AIS (complete feminization of external genitalia), partial AIS (mainly female, mainly male, or ambiguous external genitalia) and mild AIS (male external genitalia and impaired pubertal virilization). AIS is the most common disorder of sexual differentiation in individuals with 46XY karyotype. Mutations in the androgen receptor gene are found in more than 95% of individuals with complete AIS, while this occurs in 40% of partial IAS cases. Children born with complete AIS have female external genitalia, while those with partial IAS have atypical external genitalia. The characteristic features of this disorder include a female phenotype with normal breast development but absent or scanty growth of pubic and axillary hair. The disorder also includes a vagina of varying lengths along with the absence of the uterus, fallopian tubes, and ovaries. Testicular secretion of Mullerian inhibiting substance suppresses development of the uterus, oviducts, and upper one-third of the vagina in utero. Gonads in the form of testes are located at the internal inguinal ring, resides intraabdominal or can be palpable in the labia majora in children with complete AIS. Complete AIS is associated with amenorrhea and inguinal hernias in girls. The diagnosis is established with karyotype analysis, imaging studies (US, MRI) and a combination of hormonal dosages either at basal or after gonadal stimulation. There is an increased risk of gonadal tumors in patients with complete AIS. The invasive type II germ tumors encountered are the seminoma if the gonad is testis, and dysgerminoma if the gonad is considered an ovary. Seminoma is the most frequent testicular tumor in complete AIS with an age at presentation of more than 30 years. Currently, there are no clinically useful biomarkers available to guide clinicians in predicting tumorous risk other than direct gonadal histology and immunohistochemistry. If the gonads are removed due to the risk of future malignancy, hormone replacement therapy should be initiated and continued until the age of menopause. There is discrepancy regarding the timing of gonadectomy in patients with complete AIS. The consensus is to recommend delaying gonadectomy until postpubertal status is reached to allow for spontaneous puberty to develop through aromatization of testosterone into estrogen, since there is a very low risk of malignancy before puberty. Gonadectomy would necessitate initiation of hormone replacement therapy since androgens are necessary for skeletal development. Therefore, AIS patients would require estrogen replacement to achieve and/or maintain normal bone mass. Delaying

gonadectomy until patients are of an age to make their own medical decision remains safe, especially since the risk of malignancy before puberty is very low. Ultrasound surveillance should be utilized to screen patients for malignancy, should they decide to retain their gonads into adulthood.

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Anorchia

Congenital anorchia, also known as testicular regression or vanishing syndrome, is defined as the absence of one or both testes in a 46,XY individual with a male phenotype. Anorchia occurs unilateral in 97% of cases accounting for 10% of cases in which the testis is absent from the scrotum or inguinal canal. Testes are impalpable in 20% of cryptorchidism cases, with unilateral anorchia as the cause in 35-60% of them. Unilateral anorchia occurs in one of 5000 males. Bilateral or true congenital anorchia is rare, occurs in one of each 180 cases of cryptorchidism, or one in 20,000 male births. A few children with anorchia present with ambiguous genitalia or microphallus. Anorchia is a component of several malformation syndromes such as Cross syndrome, OEIS syndrome, Saldino syndrome and sirenomelia. Phenotyping into male external genitalia depends on anti-Mullerian hormone (AMH) produce by Sertoli cells and testosterone produced by Leydig cells. This means that testes were present but disappeared in utero. The genetic cause of anorchia is not known. Laparoscopy has suggested that some cases of anorchia are the result of prenatal testicular vascular accidents associated with torsion during in-utero testicular descent. Infants with bilateral anorchia present with micropenis in almost 50% of cases. Upon examination palpable testes are absent, while during laparoscopy blind-ending spermatic cord and epididymides are usually present. In children with bilateral anorchia serum testosterone concentration is very low and does not increase in response to HCG stimulation. Serum AMH concentrations are usually undetectable in patients with bilateral congenital anorchia. Inhibin B is undetectable in most boys with bilateral congenital anorchia. Undetectable levels of AMH and inhibin B, along with elevated FSH and LH levels in a 46,XY karyotype is sufficient evidence for diagnosis of congenital bilateral anorchia.

True bilateral anorchia must be differentiated from intra-abdominal bilateral cryptorchidism. Diagnosis is based on a combination of biochemical tests, karyotype, imaging studies and surgical/laparoscopic exploration. Surgical/laparoscopic exploration and histologic findings typically show nubbins of fibrous tissue devoid of any testicular tissue attached to a blind-ending vas deferens. Histopathology examination has confirmed the presence of germ cells in 0-16% of excised testicular remnants. Germ cell tumors cannot develop from a testis remnant that has no germ cell survival from the early embryonic primordial germ cells. Hence tumor development is extremely rare in remnants with germ cells. Nubbin excision should be performed if the internal ring is open with normal vessels. Management of congenital bilateral anorchia consists of testosterone replacement to stimulate penile length and induce sexual development. Testicular prostheses can be implanted in the scrotum for psychological and cosmetic reasons. Unilateral anorchia does not require hormonal management.

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Mixed Gonadal Dysgenesis

Mixed gonadal dysgenesis (MGD) is a very rare disorder of sexual development characterized by gonadal asymmetry with an abnormal dysgenetic testis on one side and a streak gonad on the contralateral side. Phenotypic features of MGD is variable, and include normal males, females with or without turner-like physical characteristic, and cases of ambiguous genitalia. Most common MGD karyotype includes a 45,XO/46,XY mosaicism. Rare mosaic karyotype identified in MGD can include 45,XO/47,XYY or 45XO/46XY/47XYY. The phenotypic abnormalities are the result of incomplete inhibition of Mullerian structures, and incomplete masculinization of external genitalia. 95% of MGD children have Mullerian remnants and 75% of streaks gonads have an ipsilateral fallopian tube. 90-95% of patients with a prenatal diagnosis of 45,XO/46XY will be phenotypically normal male. Clinically they present as children with ambiguous or abnormal genitalia, or adults with gonadal failure or short stature. Other associated problems in MGD include cardio renal malformations, gonadal blastomas and germ cell tumors. Patients with bilateral streaks are associated with the phenotype of a sexually infantile female, those with a streak and intra-abdominal testis present with clitoromegaly in a female, and those with one scrotal testis and an intraabdominal streak are associated with frank sexual ambiguity, and bilateral scrotal testis present as a male with short stature and gonadal failure. All these

cases with MGD are infertile. Diagnosis should be suspected with delay in puberty changes, short stature, webbed neck, and coarctation of the aorta. Diagnosis is established with karyotype, cytogenetic studies (FISH or PCR analysis), imaging studies (US, MRI) and laparoscopy. During laparoscopy a biopsy of each gonad should be ascertained before embarking in bilateral gonadectomy. In MGD, the gonadal phenotype ranges from streak gonads through dysgenetic to functioning testes. Congenital adrenal hyperplasia should be rule-out clinically and biochemically. In patients with MGD the sex of rearing decision is usually female. The term Y-chromosome gonadal dysgenesis is used for both 46,XY and 45,XO/46,XY karyotype with MGD. Early correct diagnosis of Y-chromosome gonadal dysgenesis has a higher potential malignant risk. The risk of developing malignancy depends on how much Y material is present. The specific location on the Y chromosome that has been identified is the gonadoblastoma location known as the GBY region. Gonadal tumor development is one of the most important challenges in patients with MGD. The most common tumor observed is gonadoblastoma, followed by invasive germ cell tumor. Gonadectomy for the Y-chromosome gonadal dysgenesis should be accomplished during the first decade of life since most tumors develop during the second decade. Neoplastic transformation of a germ cell in dysgenetic gonads, either gonadoblastoma or invasive germ cell tumor, occurs in 20-30% of 46,XY MGD patients. The child to be raised as a female will need clitoral recession and vaginoplasty in early infancy. If it is to be raised as male, then various types of hypospadias repair can be done, gonads can be replaced with prostheses, the scrotum reconstructed and Mullerian structures removed.

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