Chapter 14
46,XY Disorders of Sex Development (46,XY DSD) due to Androgen Receptor Defects: Androgen Insensitivity Syndrome

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Androgens have a fundamental role in male sexual development and act by binding to the androgen receptor (AR), which is encoded by a gene located at the X chromosome. Androgen insensitivity syndrome (AIS) is a rare X-linked disorder in which 46,XY subjects have complete or partial impairment of androgen action throughout life due to abnormalities of the AR. Subjects with the complete form of AIS (CAIS) have a female phenotype, including female breast development that begins at the age of expected puberty, primary amenorrhea, and a paucity or absence of axillary and pubic hair. Partial AIS (PAIS) causes a spectrum of phenotypes, ranging from women with clitoromegaly to men with minor degrees of undervirilization; gynecomastia is common at puberty. In both CAIS and PAIS, androgen production is in the normal male range [1].

The importance of estrogens for the pubertal growth spurt and bone mineralization, in both males and females, has been recently shown. However, the direct effects of androgens and Y chromosome-specific genes remain less clear. Patients with androgen insensitivity syndrome constitute a natural model to study the effects of Y genes, which are present, and androgens, whose action is absent.

We studied the *AR* gene in 32 subjects (20 families) with 46,XY DSD. Study criteria were 46,XY karyotype, normal male basal and hCG-stimulated levels of serum testosterone and steroid precursors, gynecomastia at puberty, and in prepubertal patients, a family history compatible with X-linked inheritance. Mutations in the *AR* were found in all 9 families with CAIS and in 8/11 (73%) of families with PAIS. We summarize here the main clinical, hormonal, bone densitometry, molecular, and behavioral features of the 25 Brazilian subjects with AIS confirmed by identification of mutations in the *AR* [2].

Nine mutations had been previously reported and six were first reported in this cohort: 87% mutations were located in androgen-binding domain; 53% mutations

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were located in exon 5 or 7 (hotspot) [2, 3]. Identification of mutations in the androgen receptor was essential to classify patients with 46,XY DSD as PAIS. The presence of a family history and/or development of gynecomastia at the time of expected puberty was useful to select patients for genetic studies and increase the likelihood of finding a mutation in the AR.

Estradiol levels were within the normal range in all patients with CAIS, and many with PAIS, suggesting that gynecomastia developed in response to normal estrogen concentrations unopposed by androgen action. Serum LH, as well as the LH × T product, was elevated in all pubertal patients indicating resistance to androgen in LH feedback. Testosterone levels were normal or elevated. Serum FSH levels were normal unless the patient had testicular damage due to cryptorchidism and/or orchidopexy.

In patients with CAIS, absence of axillary hair was more frequent than absence of pubic hair, which usually was present but sparse. In patients with female social sex, vaginal dilation was useful to obtain an adequate length for sexual intercourse. In patients with PAIS, phallic size and its response to high-dose testosterone therapy were usually subnormal, but variable among patients (adult penile length varied from 5.5 cm after 250–500 mg/week testosterone esters to 10.0 cm without treatment). All patients with PAIS raised as girls, as well as those raised as boys, maintained the gender assigned before puberty, despite an overlap in their phallic sizes at puberty. This compares with patients with 46,XY DSD due to 5α reductase 2 and 17-hydroxysteroid dehydrogenase 3 deficiencies who, in our experience, frequently change from female to male gender at puberty.

There is no consensus if height and bone density in patients with AIS should be compared to male or female standards. Patients raised as girls will be socially compared to other women; biologically they harbor Y-specific genes but lack the androgen effects of normal males.

In our cohort, patients with CAIS had an adult height of 165.7 ± 8.9 cm, corresponding to a mean SDS of –1.35 (median SDS of –1.01) for men and mean SDS of + 0.59 (median SDS of + 0.96) for women. Patients with PAIS had an adult height of 168.7 ± 9.6 cm, corresponding to a mean SDS of –0.88 (median SDS of –0.91) for men and mean SDS of +1.08 (median SDS of +1.07) for women. Therefore, adult height in patients with AIS was intermediate between that of normal males and females ($P < 0.05$) [4].

The shorter height in relation to males might have resulted from an impaired androgen action on normal male statural growth, whereas the taller stature in relation to females might reflect an androgen-independent participation of Y-linked genes in height determination.

Bone mineral apparent density (BMAD) in subjects with CAIS and PAIS submitted to gonadectomy and estrogen replacement was normal in the femoral neck but deficient in vertebral bone ($z = –1.56 \pm 1.04$, $P = 0.006$, compared to female standards; and $z = –0.75 \pm 0.89$, $P = 0.04$, compared to male standards [4]). Low spine bone mineral density before and after gonadectomy and in estrogen replacement-compliant CAIS may reflect androgen resistance at the bone level and support a direct role of androgens on bone, apart from its effects after aromatization into

estrogens. Careful follow-up of subjects with AIS and surveillance for the incidence of fractures are necessary to determine which results of bone densitometry, BMD or BMAD, and which normative references, male or female, are more informative and lead to criteria for intervention.

References

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