

## REVIEWS & COMMENTS FROM THE LITERATURE

### Androgen Insensitivity Syndrome—Ethical and Legal Implications of Genetic Testing

Berg and colleagues presented a case of a 2-month-old full-term infant with an inguinal hernia. The external genitalia were unambiguously female; however, bilateral hernias with solid structures having internal blood flow but no follicles or Fallopian structures were detected. Hernia repair revealed seminiferous tubules with germ cell hyperplasia, no vas deferens, and presence of round ligament tissue. The karyotype was 46,XY and MRI of the pelvis revealed absence of the uterus, ovaries, and a blind vaginal pouch. The diagnosis of androgen insensitivity syndrome (AIS) was confirmed by identification of a novel homozygous nonsense mutation predicted to negatively impact androgen receptor (AR) gene function. The authors then provided an informative discussion of the syndrome and its clinical management.

In the context of counseling this particular family about the heritability of AIS, testing the proband's sisters was recommended. The patient's 22-month-old sister was diagnosed with AIS; and the 9-year-old maternal half-sister had a 46,XX karyotype. A four-generation pedigree detected a significant bias toward female offspring in previous generations; 10 of the 11 individuals in the great-great-grandmother's generation were female, 5 of whom were infertile and some of whom were known to have absent ovaries, uterus, or both. There were also women in more recent generations. The authors assumed many of these women were at risk for being previously undiagnosed 46,XY females or 46,XX heterozygous carriers of the familial AR mutation who could have affected children with future pregnancies. Due to the possible health risks associated with AIS (an increased risk of testicular neoplasms, which is reportedly greatest after puberty but can occur even in the elderly, and increased risk for osteopenia), provision of genetic testing for other at-risk family members could be considered an ethical responsibility of the health care team.

The ethical aspects of diagnostic disclosure elucidated were: (1) the history of withholding information from patients with disorders of sex development (DSD) based on the assumption that physicians were better able to determine what was in the patient's best interest; (2) the principle of informed consent asserts an ethical imperative to disclose such a diagnosis to the patient; in the case of minors, participation in decision-making is guided by the concept of "assent" commensurate with developmental capacity; and (3) the extent to which a physician has the dual responsibility to maintain confidentiality and to inform other members of the family that they may be at risk for being affected by a condition or for transmitting it to their offspring. The best resolution to the latter issue is to request that the parents of the affected child disclose their child's condition to other

members of the family and ask those members to contact a physician. The authors advised, in the case of refusal to disclose information to other family members, that the clinician should carefully document discussions held with the family and to continue to encourage them to disclose information to those at risk.

Among the considerations of offering genetic testing to other at-risk family members in this pedigree, are the potential legal ramifications of a diagnosis of AIS. In a 1999 case (*Littleton vs. Prange*) involving a wrongful death suit, a court in Texas ruled that the transsexual woman's marriage to her deceased husband was invalid because of her 46,XY karyotype. This sort of ruling could extend to many areas of the law in which sex is a central issue (eg, discrimination, choice in marriage, participation in sports, housing in higher education and the penal system) and could conceivably affect individuals with common sex chromosome aneuploidy, ie, Turner syndrome and Klinefelter syndrome.

The gender medicine team involved in the present case discussed AIS extensively with the parents. Details of both physical and psychosexual development, specifically gender identity and gender role, were reviewed. Questions were answered and additional information was provided pertaining to child rearing, the rationale for gonadectomy to prevent testicular malignancy, future hormone replacement, infertility issues, and the potential for legal complications to arise. The medical team conducted an assessment of the family's understanding of the condition and its future implications. The family was also made aware of psychologists' availability for support and assistance in discussing the diagnosis with the affected girl at an appropriate age. The parents were also strongly encouraged to disclose the information about AIS to extended family members so that they could seek genetic counseling and testing, if desired.

With regard to DSD, more generally, the authors noted that in the context of current knowledge regarding the process of sex determination and differentiation, unidimensional definitions of "sex" are inherently problematic. They suggested that clinicians be prepared to advocate on behalf of affected patients when caught in legal predicaments, perhaps in the form of an *amicus curiae* from the American Academy of Pediatrics.

Berg JS, French SL, McCullough LB, et al. Ethical and legal implications of genetic testing in Androgen Insensitivity Syndrome. *J Pediatr*. 2007;150:434-8.

**Editor's Comment:** *The reader can find additional guidance regarding the friction between the principles of confidentiality and disclosure of genetic information*

in 2 recent reports.<sup>1,2</sup> The authors of the current case report do not inform us whether the family in question gave consent to disclose the patient's diagnosis to at-risk extended family members. Regardless of whether they did or not, the "gender team" should be commended for delivering care to the family in a manner consistent with the recent Consensus Statement of Management of Intersex Disorders.<sup>3</sup> The process of disclosing all aspects of the DSD and its clinical care should be collaborative, on-going, and planned with the parents from the time of diagnosis. But, what if the family in this case refuses to allow disclosure to other, potentially affected family members? The 1983 President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research<sup>4</sup> provides some valuable guidance. For example, it states that when the patient refuses, a health care professional's disclosure to at-risk family members should take place only when: (1) reasonable efforts to elicit voluntary consent to disclosure have failed; (2) there is a high probability that harm will occur if the information is withheld, and the disclosed information will actually be used to avert harm; (3) the harm that would result to identifiable individuals

would be serious; and (4) appropriate precautions are taken to ensure that only the genetic information needed for diagnosis and/or treatment of the disease in question is disclosed. Approximately 10 years later, the Committee on Assessing Genetic Risks of the Institute of Medicine<sup>5</sup> added an additional criterion: that there is no other reasonable way to avert harm. Neither group implied that the clinician has a legal duty to inform relatives, instead arguing for an ethical duty and legal permission to inform in certain cases.

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## References

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4. United States. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Screening and Counseling for Genetic Conditions: A Report on the Ethical, Social, and Legal Implications of Genetic Screening, Counseling, and Education Programs. Washington, DC: U.S. Government Printing Office; 1983.
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## CAH Women: Sexual and Reproductive Outcomes

Gastaud et al performed a cross-sectional study using face to face interviews, written questionnaires, the Female Sexual Function Index (FSFI), a brief self-report measure of female sexual function, and a gynecological examination in 35 women aged 18 to 43 years with congenital adrenal hyperplasia (CAH), presenting Prader stages I-V at birth who had been treated from birth to adolescence in the same pediatric endocrine clinic. The objectives of the study were to obtain a detailed description of sexual and reproductive outcomes in adult women with CAH and to compare these outcomes among CAH subtypes and with non-CAH controls. Fourteen of the CAH patients had presented with severe masculinization of their external genitalia at birth (11 with Prader IV and 3 with Prader V stages).

None of the patients expressed doubts about their gender assignment. At gynecological examination cosmetic and anatomic outcomes were considered good by both the patients and the examiner, and 65% of the subjects presented with a satisfactory clitoris, introitus and vagina. However, 9 of 35 patients (26%) were diagnosed with vaginal stenosis, 6 of these belonging to the Prader IV-V group at birth. Seven subjects (20%) reported homosexual inclinations, compared with 5.7% in the control group and 6.6% in a large survey of age-matched women in France (ACSF) and these tendencies were present in 43% (6 of 14) of the Prader IV-V women. A decrease in sexual function was noted when the 35 CAH patients were compared with the 69 healthy controls utilizing the FSFI questionnaire, thus 37% (13 of 35) reported

never having sexual intercourse with vaginal penetration by their partners compared with 5% in the ACSF survey. Of these women, 8 attributed their lack of sexual intercourse to the anatomy of their genitalia, 2 believed intercourse would be painful and/or 7 had no partner; the 3 patients born Prader V were among this group. Some degree of pain during vaginal penetration was experienced by 56%, 9 of them presented with moderate or marked stenosis of their introitus. Eight patients cohabited with their partner or were married and 77% wished to be pregnant in the near future or at a later time. Eight subjects became pregnant, only one in the Prader IV-V group; however, only 17% (6 of 35) had children compared to 71% of French women in the ACSF survey. The authors concluded that despite the expert medical and surgical care received by these patients, women with CAH suffer major limitations in their sexual function and their reproductive life.

Gastaud F, Bouvattier L, Duranteau L, et al. Impaired sexual and reproductive outcomes in women with classical forms of congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2007;92:1391-6.

**Editor's Comment:** Female neonates with CAH may present with some degree of masculinization of their external genitalia at birth and those with severe virilization (Prader stages IV-V) may require extensive surgery to correct for different degrees of clitoral enlargement and labio-scrotal fusion. In addition, many may develop chronic masculinization as a consequence of being exposed to an excess of adrenal androgens postnatally, with the development of hirsutism, acne, muscle