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Late Diagnosed 46,XX Child with Congenital Adrenal Hyperplasia (CAH): Deciding the Gender of Rearing

To the Editor:

Yeşilkaya et al.¹ presented an interesting case of “A 46XX Disorder of Sex Development [DSD] with a Prostate Gland and Increased Level of Prostate-Specific Antigen” who was born with complete masculinization of the genitalia (Prader stage 5 of genital development) and reared as a male. It was not before 5 years of age that this child was correctly diagnosed as genotypic female with simple virilizing congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency, on the basis of a 46,XX karyotype, the presence of a uterus and ovaries, and the necessary hormone tests. The diagnosis raised the question of the appropriate gender assignment. Apparently on the basis of the family’s wishes for continued rearing as a male, plans were made for a hysterosalpingo-oophorectomy and insertion of prosthetic testicles. However, in contrast to the detailed documentation of medical findings, no data were provided on the gender development of this child. The maintenance of male rearing in this case entails the induction of iatrogenic infertility, which certainly poses an ethical dilemma.² At the very least, a careful gender work-up is needed to justify such a decision.

It is by now well established for mammals in general, including humans, that the development of gender-related behavior during the juvenile period and at later ages depends to quite an extent on the sexual differentiation of the brain brought about by the action of sex steroids during hormone-sensi-

tive, prenatal or perinatal periods of development, in addition to or in interaction with various genes.^{3,4} In humans, the available evidence points to the prenatal period as the primary one in this differentiation process,⁵ although later social and psychological factors may further modulate gender-related behavior.⁶ Data on girls and women with CAH show an association of the degree of prenatal androgenization (and genital masculinization at birth) with the degree of behavioral masculinization later, but the strength of this association is only modest.^{7,8} One also has to consider that the genetic and hormonal factors involved in the sexual differentiation of the brain overlap with, but are not identical to, those involved in genital differentiation. Thus, inferring the degree of brain and behavior masculinization from the degree of masculinization of the genitalia has very limited validity.

The development of gender *identity* is even much less directly related to the prenatal hormonal milieu.^{7,9} The fact that the prevalence of gender dysphoria and gender change vary widely between DSD syndromes suggests at least some indirect association with gross variations of the degree of prenatal androgen exposure of the brain in interaction with brain-development genes. Yet, although gender dysphoria and/or patient-initiated gender change in DSD patients typically occur in association with gender-related behavior that is markedly atypical for the patient’s gender assignment, many patients with the same degree of atypical gender behavior develop a gender identity commensurate with their assigned gender.

Certainly, parental wishes do not firmly determine long-term gender outcome. Case reports show that gender reassignment imposed after infancy by parents and physicians can lead to strong resistance on the part of the patient, and to gender dysphoria and/or patient-initiated gender re-assignment later. There-

fore, already the intersex-management policy developed at Johns Hopkins Medical Center in the 1950s and 1960s strongly advised against such late-imposed reassignment, unless desired (without coercion) by the patient, and this recommendation was repeated in the recent International Consensus Conference on the Clinical Management of DSD.¹⁰

In regard to the syndrome discussed here, 46,XX newborns with (undiagnosed) CAH who are markedly masculinized (Prader stages 3–5) may be erroneously assigned to the male gender, which occurs more frequently in populations without easy access to specialized medical services.¹¹ If such children survive, they may develop a male gender identity during the preschool years and maintain it in adolescence and adulthood, even if they are finally diagnosed correctly. However, a significant minority develop gender dysphoria and/or change their gender, at a rate comparable to that seen in 46,XX raised females, as was documented in a recent review of the world literature in preparation for the International Consensus Conference on Intersex in 2005.¹² As a group, 46,XX patients with the simple virilizing variant of CAH show only a mildly elevated behavioral masculinization,^{7,8} which further complicates the prognosis of gender identity development.

Clinically useful imaging methods for the direct ascertainment of the sexual differentiation of the brain during infancy or later are not yet available. Instead, the systematic evaluation of gender-related behavior and gender identity/dysphoria is crucial as a basis for decisions on gender assignment and reassignment after infancy.¹⁰ A number of systematic psychological assessment methods have been developed for this purpose.¹³ In my clinic, for instance, we use a multimethod approach to assessment involving a standard set of systematic questionnaires and structured interviews with parents

and child separately, as well as systematic observation of the child's play with a standard set of boys' and girls' toys.¹⁴ A team in Ankara, Turkey, has established a similar approach to such gender decisions,¹⁵ which I would strongly recommend for the patient discussed here.

In summary, in line with the recommendations of the International Consensus Conference¹⁰ and its background literature, a systematic evaluation of development of gender-related behavior and gender identity/gender dysphoria should be performed as a basis for decisions on continuation or change of gender of rearing in late-diagnosed children with DSD.

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