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Case Report

Adult Outcome After Partial Androgen Insensitivity Syndrome: Diagnosed and Assigned Female in Infancy

Peter A Lee. Adult Female Outcome After pAIS Diagnosis in Infancy

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What is already known about this diagnosis?
Partial Androgen Insensitivity Syndrome (pAIS) is a diagnosis in which there is a defect in androgen action related to a mutation of the Androgen Receptor, binding of the androgen to the receptor, or other defects which have not yet been prescribed. Most individuals with pAIS have been assigned male in spite of infertility based on limited outcome data. Extent of masculinization at puberty can not be predicted, penis size is commonly diminished, and adult quality of life has been inadequately reported among males and females.

What this report adds?
The individual diagnosed with pAIS reported here was assigned female as an infant and currently is older than 40 years of age and has an excellent quality of life, considering all aspects including marriage, sex life, larger family and friends, and career, demonstrating in this instance that female assignment was appropriate.

ABSTRACT
This patient, now in her 40s, was evaluated because of genital ambiguity and diagnosed with pAIS in infancy based upon elevated testosterone and gonadotropin levels and significantly reduced binding affinity of the androgen receptor. Such reduced binding is consistent with a structural abnormality of the receptor protein precluding expected activity of the androgen receptor. Based on this information and counseling, her parents chose a female sex assignment. She had clitoral recession and testes removal as an infant and neovaginal surgery using a distal ileum segment at age 11 years and was begun on estrogen therapy at age 12 years. She is being reported now to point out that the data known at her birth provided as specific information to guide sex assignment and genital surgery as is currently available. More importantly, long-term outcome data is very positive showing clear female gender identity, successful marriage of more than 20 years, excellent social relationships including family and friends, an active social life. Since this diagnosis is lifelong, it is inevitable that there will be reminders, hopefully rare, that may be traumatizing. Unfortunately, in this patient, such reminders have been related to access to health care.
Keywords: pAIS-partial Androgen Insensitivity syndrome, cAIS-complete Androgen Insensitivity Syndrome, gender identity, quality of life, masculinized genitalia

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INTRODUCTION

Categories of Androgen Insensitivity Syndrome are complete, partial or mild (1,2). The complete form is characterized by female genitalia, no Mullerian derived structures, and lack of response to testosterone during fetal and pubertal periods with female sex assignment. The partial form presents with partial masculinization of the external genitalia, testes and lack of Mullerian derived structures. Those with predominantly male genitalia are raised as males while , because of the complexity, sex assignment forthose with ambiguous may be male or female.is complex. This difficulty is because gender development, extent of prenatal exposure of the central nervous system to androgen, and extent of somatic response to androgen at puberty cannot be predicted. These categories should not be confused with Mild Androgen Insensitivity Syndrome which presents in males at puberty or later (3). Mutations have been described that result in complete Androgen Insensitivity Syndrome (cAIS), while mutations associated with pAIS fail to predict somatic responses to androgen (1,2). Binding defects in the absence of mutations and co-regulators (activators and expressors) may suggest varying degrees of poor response. Thus, whether or how much masculinization will occur at puberty cannot be predicted.

Phenotypic variation of pAIS among those raised male has been long recognized (4) with penile size outcome ranging from low normal to below the normal range (5) with fertility being unlikely. These factors make parental decisions concerning sex assignment and surgery very difficult. The patient reported here was born before mutations were identified for the Androgen Receptor gene with 46,XY. During those decades, many patients with 46,XY, testes and ambiguous genitalia were diagnosed with pAIS, although this diagnosis was not verified by hormone levels and genetic mutations. More recently, known mutations of the Androgen Receptor gene associated with pAIS do not predict potential somatic response to androgen(6). The data for this patient included elevated testosterone (T), LH and FSH levels in infancy and lack of androgen binding to skin fibroblasts in culture, which together with counseling led the parents to assign this individual as female. The purpose of this report is to verify the successful outcome for this individual now more than 40 years of age, but also contains a warning regarding this lifetime condition.

CASE REPORT She was the first patient with pAIS reported during infancy because of elevated testosterone, LH and FSH levels, normal androstenedione and dihydrotestosterone levels. In addition, there was evidence of failure of binding of androgen to the androgen receptor in cultured genital skin fibroblasts (7). She presented with a fused scrotum containing testes with 2 cm. volume bilaterally, an enlarged phallus and peritoneal urethra. This report presents the adult outcome of this individual. She is currently in her 40s and is very positively adjusted but also at rare times has intense emotional responses to overwhelming situations focusing on her condition. Sadly, there have been primarily related to current access to health care.

Her parents chose a female sex of rearing and initial surgery included removing the testes, clitoral recession and labio-scrotal reduction. During childhood, she was seen by an endocrinologist (author) infrequently until the age of puberty. Her parents gradually informed this girl of her diagnosis as the opportunity presented itself. For example, when she mentioned having children, the parents told her that not all girls are able to get pregnant and discussed other options for parenthood. Her parents indicate that she never showed "any hint of male tendencies", and always behaved, acted and talked as a girl. She has always had both male and female friends including intimate female friends, and did very well in school, social activities and sports.

Further surgery was done at age 11 years creating a vagina from the distal ileum and triangular flaps from the peritoneum. She appeared to fully grasp explanations regarding the need for surgery. Oral estrogen therapy (Premarin) was initially begun at age 12 years and therapy was switched to birth control pills after 2 years. As a teenager, she found it awkward when her female friends shared that they were having menses and often pretended that she also was having a period. Before 18 years of age, she knew her karyotype and that she was born with testes and an enlarged phallus. This patient was followed by the author until her late teens and he has since been in contact. When he last saw this individual as a teen, she said he made her feel "like a person" after she was told that if she went out on the street and looked at 10 girls that no one would see anything different between her and them. She also was reminded that she was born with a condition that is lifelong, she will periodically have unwelcome reminders.

OUTCOME AND FOLLOW-UP

Currently she describes herself as happy, healthy, working as a licensed veterinary nurse and living with her husband of more than 20 years, and had a good sex life. As occurs with neovaginas created from the distal ileum, there is mucous secretion for which she wears a panty liners daily. She indicates that overall her life has been good, that she is thankful for her family, and a really good family of friends. She has always identified with female gender identity; never felt masculine but always felt awkward when thinking about her karyotype. This is in spite of realizing that her body could not respond to the testosterone because of a dysfunctional androgen receptor, including lack of fetal brain differentiation changes that result from testosterone. She had been told that impact of fetal androgen exposure is not understood, but likely impacts gender development, cognitive functions and sexuality.

Her father, a retired psychology professor, indicates that he always had "traditional values". He and his wife have always felt that they made correct decisions during infancy and childhood for this daughter and have remained very close to her even though she moved a considerable distance away. She has 2 sisters, who are 2 and 4 years younger, who do not have pAIS. They are married and have children. Both had prenatal evaluation and were told that their children would not have pAIS.

Her father indicates that their oldest daughter has a temperament that is happy-go-lucky, an analytical mind and is intense. She has a good sense of humor, making family times very pleasant. But she has rare times that are still hard and may result in panic attacks. An example is a consequence of having to change health care when she moved and see a different physician. This physician who assumed she was simply requesting birth control pills indicated that she would need to get a PAP and other testing. She was overwhelmed with the need to tell this physician about her full history and did not get the tests ordered and as a consequence went without estrogen therapy for several years, after having taken replacement therapy for about 15 years.

Almost two-thirds of AR mutations are in the ligand-binding domain. About one third are within exon 1 (most being truncated) and 8. Most missense mutations are in exons 4 to 8. PAIS usually presents with hypo-masculinized external genitalia in 46,XY individuals associated with mutations of the androgen receptor gene (AR) and/or inability of the receptor to bind testosterone resulting in varying degrees of inability of tissues to respond to testosterone. These degrees vary from essentially lack of any response as seen in cAIS, to very good responses. A series of 10 AIS individuals included 9 asssigned cAIS and one pAIS (6). None had had their LH, FSH or T measured during the first 2 years of life. Nine had testes and one a rudimentary ovary, excluding the diagnosis. The mutation in the individual assigned pAIS, who had a descended and a inguinal testes and hypospadias, had a base change in exon 3. Another report was from a survey regarding risk of gonadal germ cell cancer included 166 cAIS women and 26 pAIS men (8). This and the subsequent reports illustrate the lack of outcome data for pAIS patients raised either male (the majority) or female. A report exploring prognostic indicators to aid decision making for pAIS patients included 27 patients all assigned male by comparing external masculinization scores < or > 5 (9). They found that all 18 individuals with a score >5 had spontaneous puberty while only 6 of 9 <5 did. Among those <5, 4 patients who had fused scrota and descended testes (similar to the case reported here) had spontaneous puberty although stage 4 to 5 genitalia did not occur among the only 2 for which this was reported. It is not clear whether raising these latter individuals as female would have resulted in better adult outcomes. A commentary (10) indicates that further studies are necessary to determine if there are predictors regarding sex assignment and other care issues.

DISCUSSION

There continue to be no clear guidelines for sex assignment in pAIS (2). It is of interest that this publication which discussed only those who had ambiguous genitalia, made no comparison with those born essentially male raised male. More reports are needed of those raised female, in addition to the good outcome of the individual reported here. However, since there was genital ambiguity, it will remain unknown if there would have been a response to androgen at puberty. Also, it is impossible to ascertain extent of T binding in the CNS during fetal life. Because the high T, LH and FSH indicating lack of androgen binding in the hypothalamus or pituitary, measuring LH, FSH and T could be advocated on several occasions during the first month of life noting the age of sampling should precede the increase of testicular testosterone secretion peaking at about 6 weeks of life, commonly referred to as minipuberty.

Adult outcome information found that the individual reported herein is well-adjusted and functions exceptionally well with an excellent good quality of life, except for very rare occasions. These occasions, not surprisingly, occurred when she was place in awkward situations regarding her lifelong congenital condition.

The negative aspect of this individual's adult life occurred after she moved with her husband a considerable distance from her health care location. Her attempt to enter a system covered by her insurance required that she see a primary care worker who failed to perceive that she was not a typical patient asking for birth-control pills. This medical caretaker insisted that a PAP smear and other blood testing be done before renewing the medication. This precipitated what the patient described as a "meltdown", feeling that the trauma would be worse if she told this primary care worker about her karyotype and genitalia at birth. This likely resulted in a possible risk because she did not take any estrogen replacement therapy for years afterward, when I encouraged her to see an adult endocrinologist. This issue involves both the chronic problem of transfer of complicated pediatric endocrine patients, especially those with DSDs to internal medicine or gynecologic endocrinologists and the current method of acquiring medical care.

CONCLUSIONS

Patients with pairs assigned female with adult outcome with similar findings in the individual as a newborn can have well-adjusted adult life, in spite of infertility. Advantages include an early clear diagnosis, good care included counseling with support of a spouse/partner, family and friends and a fulfilling career. However, rare conditions, such as pails persist for a lifetime so patients with such diagnoses will have periodic

reminders, which, depending upon the situation, may be traumatic. The current care model in North America involving entering a new health care system, via primary health care workers, carries a risk of care takers being unaware of such rare diagnoses resulting in much trauma.

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Ethics: Informed consent has been obtained from the patient and her family.

Author Contribution
The author, who diagnosed and cared for this patient until late teens and has maintained contact since, wrote this manuscript from that knowledge, medical records and discussions with the patient and her parents.

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