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Special Article – Androgen Insensitivity Syndrome

Complete Adrogen Insensitivity, Mayer-Rokitansky-Küster-Hauser and Misdiagnosis

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Abstract

Diagnosis of a two-day-old healthy infant with CAIS leads to the same diagnosis in two of the three other sisters; one of whom was misdiagnosed for years as MRKH. Discussed are the ramifications of the misdiagnosis and the best practice for the care of these individuals, which includes psychological support, education and meeting others. Best practice also includes the challenge of when to educate and test the fourth girl, age 11 not diagnosed but could be a carrier.

Keywords: Complete Androgen Insensitivity Syndrome (CAIS); Mayer-Rokitansky-Küster-Hauser (MRKH); Gender identity; Androgen insensitivity

Case Presentation

A full term infant, announced as a girl, was transferred to our hospital by the infant's pediatrician when informed by the mother that a prenatal test indicated 46, XY. Following our hospital's established protocol [1] involving a team approach to infants born with Disorders/Differences of Sex Development (DSD), I went to the hospital to meet the parents. Also present was the 21 year-old half-sister, same mother different father. At home were two other sisters and one older brother. The father was visibly upset that his healthy baby was transferred with no reason given.

I explained why we were not assigning a gender to their baby, even though announced as a girl. We referred to their infant as "baby." With the use of diagrams [2], I explained sexual differentiation and development of the internal and external sexual reproductive system. I explained the possible diagnoses. I identified the other team members who would be examining their baby and their medical specialties. They would receive all medical information relevant to diagnosis once all results were available but not before in order to avoid a false conclusion as to diagnosis and gender assignment. At that point, they would become team members helping to decide the gender announcement of their baby.

Parents asked about the chances for fertility. I mentioned that fertility in some diagnoses was an issue because of various problems (e.g. absence of a uterus, dysfunctional gonads). I noticed the 21 year-old half-sister crying. She said, "That is me." She had been diagnosed at age 18 with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. At age 22, she underwent a vaginoplasty using bowel. She had received very little education about her diagnosis. I offered to explain the diagnosis to her and answer any questions.

The genetic mutation c.2325>A (p. Arg 775His) was identified confirming the infant had the CAIS diagnosis. The DSD team and the parents agreed to keep the initial gender of announcement; "It's a girl." I provided more education to the mother. The father did not attend sessions. Karyotype testing of the other two sisters revealed that one sister was 46, XY.

I obtained the surgical records as well as records from the physician who made the MRKH diagnosis in the 21 year-old half-sister. There was no record of a karyotype. Karyotype testing revealed 46, XY. The misdiagnosis of MRKH was changed to the correct one, CAIS. We informed the mother who informed her daughter.

In summary, three of the four girls were diagnosed with CAIS. All the children had the same mother. Only the half-sister had a different father. I met with all of the girls and their mother to provided support and education. I also suggested that the family attend an annual convention of Androgen Insensitivity Syndrome and Differences of Sex Development (AIS-DSD), a nationally known support group for persons diagnosed with androgen insensitivity and their families.

Discussion

MRKH, the second most frequent cause of amenorrhea after gonadal dysgenesis is an uncommon congenital anomaly of 46, XX woman with functioning ovaries and, normal external genitalia [3]. It is estimated to occur in approximately one in every 5,000 women. Features include vaginal agenesis and uterine abnormalities that range from an absent uterus to rudimentary uterine remnants. Adolescence is usually the time it is diagnosed due to primary amenorrhea.

Androgen insensitivity is an X-linked disorder of 46, XY differentiation. The result is an absent or defective Androgen Receptor (AR) gene which impairs utilization of androgen from functioning testes. Two forms of androgen insensitivity: Partial Androgen Insensitivity Syndrome (PAIS) and Complete Androgen Insensitivity Syndrome (CAIS) occur. All individuals with CAIS present with female-typical external genitalia [4]. Internally, there are no Müllerian structures, such as a uterus, proximal vagina, due to the effects of the anti-Müllerian hormone secreted by the testes, along with testosterone and estradiol. The distal vagina is usually short, dimple-like, with a blind ending. If the testes are not removed before puberty, their (normal) estradiol production will result in the development of breasts. Diagnosis is usually made in adolescence due to primary amenorrhea. Even through the risk of cancer is low, recent research suggests that gonadectomy may be deferred until adulthood due to the low risk of malignancy. There is analgorithm to help guide

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clinicians in management of patients with CAIS who have deferred gonadectomy [5]. Once removed life-long estrogen replacement is required. All individuals diagnosed with CAIS are gender announced as girls. Reports of self-gender change in CAIS are rare but have been reported [6]. The majority of individuals diagnosed with CAIS identify as females, which is what they were gender assigned at birth [7]. In contrast, gender announcement of infants with PAIS is difficult and can be either boy or girl due to the ambiguous appearance of the external genitals. There is not a single report of an individual with MRKH self-gender changing to male.

Consequently, in adolescence and adulthood, initial presentation can be similar in persons with MRKH and CAIS: amenorrhea, lack of a uterus, a shortened vagina in a woman with breast development. The half-sister was misdiagnosed with MRKH because gonads seen on ultrasound were read as ovaries and no karyotype was performed until years later when her infant sister was diagnosed with CAIS. Karyotype is vital in distinguishing between MRKH and CAIS. The misdiagnosis had significant ramifications. This young woman thought she had functioning ovaries and the typical female sex chromosome pattern. She was unaware that she had testes, which in time may become malignant if not removed. She was aware that she could not become pregnant because she did not have a uterus but she was under the impression that her "ovaries" were functioning and could produce eggs that may be used to produce a child *via* artificial reproductive technologies. Despite living for 21 years as a female, her first response to the correct diagnosis was "I am a boy", which confirms the power of chromosomes in people's thinking despite knowledge that gender is not solely determined by sex chromosomes.

Any significant role of an XY karyotype on gender identity development remains speculative. 46, XY women with Complete Androgen Insensitivity Syndrome (CAIS) show brain responses to sexual images similar to 46, XX women, and markedly different from XY men, with whom they share a Y chromosome and a high prenatal and infant testosterone secretion [8].

The second lesson learned is that proper care of individuals with these diagnoses does not end with diagnosis, as one physician said, when speaking about MRKH, "It's more than the anatomy" [9]. Best practice includes psychosocial management, which focuses on gender development and sexually related aspects of care but also other quality of life domains [3,10].

I provided education and support to the half-sister and her sisters and their mother. Informing children of their condition is beneficial [11]. The issue is no longer whether or not to disclose, but when and how to tell. For years, parents, despite fears, agreed that their children had the right to know the full details of their DSD condition, treatment, and that the information given in stages [12]. Such a systematic approach was outlined [13] and today there are many educational resources, some for specific DSD conditions, for children, adolescents, and young adults. (e.g.www.accordalliance.org). This link also has a list of support groups by specific DSD condition. I referred them to a national support group annual conference which they attended. They met other parents and their children and adults with the same diagnosis. They reported that it was extremely helpful, even for the 11 year-old girl who did not have CAIS. However, this child could be a carrier of the gene mutation. The challenge was when to inform her that she could carry the mutation.

Conclusion

Karyotype is critical to distinguish between MRKH and CAIS. Misdiagnosis will result in miseducation, false hopes, and possible future serious medical consequences. Proper diagnosis does not insure best standard of care. This requires addressing the psychological needs of the patient upon hearing the diagnosis.

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