

Etiology Unknown in Most XY Disorder Patients

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CHICAGO – Etiology remains elusive in many patients with disorders of sexual development, according to data from one of the largest cohorts reported to date.

The analysis found that most patients with an XX disorder of sexual development (DSD) have an etiologic diagnosis,

VITALS

Major Finding: An etiologic diagnosis was made in 87.5% of patients with an XX disorder, but only 29% of those with an XY disorder.

Data Source: Ten-year retrospective analysis of 199 patients with disorders of sexual development.

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but that more than two-thirds of those with an XY disorder have only an anatomical diagnosis.

“We as clinicians should be aiming for an etiological diagnosis rather than an anatomical diagnosis in such patients to provide better care,” Dr. Karamdeep Bhullar said.

Recent consensus guidelines stress the importance of early diagnosis and coined the term DSD to describe any congenital condition in which the development of chromosomal, gonadal, or anatomical sex is atypical (Arch. Dis. Child. 2006;91:554-63). Although most cases of DSD are identified in infancy, individuals with normal male or female genitalia and discordant internal anatomy are often not identified until adulthood. A girl might present with primary amenorrhea in the case of vaginal agenesis or present with inguinal hernia that is actually testes in cases of complete androgen insensitivity syndrome, said Dr. Bhullar of the department of pediatrics at the University of Melbourne.

She presented an analysis of 199 patients, born between 1999 and 2008 and managed at the Royal Children’s Hospital in Melbourne, one of the world leaders in DSD research. In all, 107 (54%) presented with XY DSD, 64 (32%) with XX DSD, and 28 (14%) as sex chromosome aneuploidy DSD. A definitive diagnosis was made in only 57% of the cohort, Dr. Bhullar said.

An etiologic diagnosis was made in 87.5% of patients with XX DSD, but only 29% of those with XY DSD.

Of the XY children, 92% were raised as males and 8% as females, while only one (2%) XX DSD child was raised as a male. Of the chromosome aneuploidy DSD children, 68% were assigned female sex and 32%, male sex.

The consensus guidelines stress that all children with DSD should receive a sex assignment, and that evaluation and long-term management should be car-

ried out at a center with an experienced multidisciplinary team. Senior author Dr. Garry Warne, director of Royal Children’s Hospital International, Melbourne, said that early assignment of sex is thought to be the best way to prevent psychosocial harm to the child. In addition, there is a significant risk of gonadal malignancy in 46, XY DSD and sex chromosome aneuploidy DSD when there is a Y chromosome. In two conditions –

partial androgen insensitivity syndrome and Y chromosome–positive gonadal dysgenesis – the risk of cancer is around 50% if the gonad is intraabdominal.

“If the decision is made to retain a gonad in such circumstances, it is essential that a risk-management strategy be prepared and clearly communicated to the patient,” Dr. Warne said in an interview. “This is done to prevent physical harm to the patient.”

In the current analysis, the spectrum of diagnoses among children raised as males included cloacal and bladder exstrophy (17%), partial/mixed gonadal dysgenesis (6%), Klinefelter syndrome and its variants (4%), ovotesticular DSD (2%), testicular regression syndrome (2%), and partial androgen insensitivity syndrome (1%). An anatomical diagnosis without a definitive etiology was made in 68% of these patients, Dr.

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Important Safety Information

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Important Safety Information, continued

Warnings

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Due to the short duration of action of Humalog, patients with type 1 diabetes also require a longer-acting insulin to maintain glucose control (except when using an insulin pump).

Glucose monitoring is recommended for all patients with diabetes.

The safety and effectiveness of Humalog in patients less than 3 years of age have not been established. There are no adequate and well-controlled clinical studies of the use of Humalog in pregnant or nursing women.

Bhullar said.

The most common diagnosis among children raised as females was congenital adrenal hyperplasia (CAH) (47%), followed by Turner syndrome and its variants (18%), cloacal and bladder exstrophy (12%), and ovotesticular DSD (6%). Other less common diagnoses included complete androgen insensitivity (CAIS) (4%), complete gonadal dysgenesis (1%), and partial/mixed gonadal dysgenesis (1%). About 11% of those raised as females had an anatomical diagnosis without any etiology established, she said.

Except for certain conditions such as

CAH and CAIS, a female sex rearing is strongly preferred based on long-term outcomes, Dr. Warne said. For most other conditions, there are either insufficient long-term outcomes data or the diagnosis is so uncertain that it is impossible to be sure how things will turn out.

During a discussion of the analysis, an audience member said the data provide a good starting point for research aimed at better classifying these disorders, but pointed out that contention still exists regarding the consensus guidelines and the inclusion of isolated hypospadias

with palpable gonads and the placement of coital entropies in the labial adhesion category.

Dr. Warne said it is important for guidelines to be evidence based as far as possible, and acknowledged that mistakes have been made in the past, resulting in postoperative gender dysphoria that is extremely difficult to treat and leaves many patients, understandably, feeling deeply aggrieved.

"There are movements dedicated to opposing what is perceived to be current medical practice," he said. "Having said that, the medical profession accepts that

practices need to change, and is trying very hard to develop protocols that better protect the best interests of patients."

The researchers published a set of ethical principles for the management of infants with DSD (Horm. Res. Paediatr. 2010;74:412-8) that were endorsed by the Fifth World Congress on Family Law and Children's Rights, and are looking to test the principles in Australia and other cultural settings. They also are studying new methods of molecular diagnosis using Next-Gen Sequencing and gene chip technology that may provide swift and accurate diagnoses, he said. ■



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Important Safety Information, continued

Warnings, continued

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Important Safety Information, continued

Other Side Effects, continued

neuropathy or renal impairment, are using potassium-lowering drugs, or taking drugs sensitive to serum potassium level).

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