Mixed gonadal dysgenesis and Denys-Drash syndrome: urologists should screen for nephrotic syndrome

Oleg Shapiro, MD,[1] Thomas R. Welch, MD,[2] Maryellen Sheridan, MD,[1] Susan Stred, MD,[2] Jyoti Upadhyay, MD[1]

[1]State University of New York, Upstate Medical University, Department of Urology, Syracuse, New York, USA
[2]State University of New York, Upstate Medical University, Department of Pediatrics, Syracuse, New York, USA

SHAPIRO O, WELCH TR, SHERIDAN M, STRED S, UPADHYAY J. Mixed gonadal dysgenesis and Denys-Drash syndrome: urologists should screen for nephrotic syndrome. The Canadian Journal of Urology. 2007;14(6):3767-3769.

Objective: *We present a child with Denys-Drash syndrome recognized after surgery for mixed gonadal dysgenesis, and discuss screening procedures the urologist should consider in similar circumstances.*
Case report: *A 1-year-old child with XY gonadal dysgenesis underwent genital reconstruction. The postoperative period was complicated by incisional drainage, which led to the recognition of a nephrotic syndrome. Molecular analysis of the WT-1 gene confirmed a mutation associated with the Denys-Drash syndrome.*
Conclusion: *The Denys-Drash syndrome should be suspected in children with XY gonadal dysgenesis. The presence of urine protein should be sought in such children, and if present, consultation with genetic and nephrology specialists is warranted.*

Key Words: WT-1, Denys-Drash syndrome, gonadal dysgenesis, kidney failure, nephrotic syndrome

Introduction

Disorders of sex development (DSD) encompass a rare group of disorders which present in the neonatal period with ambiguous genitalia. The most common cause of ambiguous genitalia in the newborn is congenital adrenal hyperplasia (CAH).[1] Other causes include an extensive spectrum of gonadal dysgenesis including mixed gonadal dysgenesis and ovotesticular DSD (true hermaphroditism). Distinguishing these categories of DSD conditions may be difficult, and often requires histological confirmation.

Denys-Drash syndrome is a rare condition first described by Denys et al, in 1967 and was identified in a patient with 46.XY karyotype by Drash.[2,3] The entity includes the triad of 46, XY DSD, progressive nephropathy with ultimate renal failure, and an association with Wilms' tumor.[4] Mutation in the zinc finger domain of the WT1 gene is responsible for the syndrome in 95% of cases.[5] Since these patients are also at risk for developing gonadoblastoma, gonadal excision is recommended.[6]

Accepted for publication September 2007

Address correspondence to Dr. Jyoti Upadhyay, Department of Urology, 750 East Adams Street, Syracuse, NY 13210 USA

The nephropathy is usually diagnosed in infancy, and rapidly leads to nephrotic syndrome. Renal histology shows diffuse mesangial sclerosis, and deterioration to end stage renal disease (ESRD) is the usual outcome.[7]

We report a child in whom Denys-Drash syndrome was not diagnosed until she presented with a lymphatic leak following total genital reconstruction for mixed gonadal dysgenesis. We review the literature and salient features of gonadal dysgenesis associated with Denys-Drash syndrome. Since the urologist may be the first specialist to evaluate and treat some of these children, knowledge of this syndrome and its diagnosis is crucial to minimize operative complications and plan further monitoring. To date, there are no recommendations in the urologic literature as to appropriate metabolic workup of patients with mixed gonadal dysgenesis.

Patient and results

A 6-month-old child was referred from the Pediatric Endocrinology service to the Pediatric Urology service for evaluation of ambiguous genitalia. The child was born at term, and underwent DSD workup shortly after birth. No metabolic abnormalities were identified. However, karyotype showed the child to be 46, XY. Stimulation with HCG generated a poor testosterone response. Hormonal patterns were not consistent with complete gonadotropin deficiency, total or partial androgen insensitivity, or 5-alpha-reductase deficiency.

On physical exam, the patient was found to have a prominent phallus, empty asymmetric scrotal folds, hypospadic urethra at the phallus-labial junction and a separate vaginal introitus. A mobile nodular structure was identified in the right inguinal canal, consistent with an undescended testicle.

Based on genetic studies and physical exam findings, the presumptive diagnosis of 46, XY mixed gonadal dysgenesis was made, with a less likely possibility of ovotesticular DSD. Radiological studies, including ultrasound and MRI of abdomen and pelvis were inconclusive as to the presence of the uterus, fallopian tubes, or ovaries. The family, with multidisciplinary team input, decided to rear the child as a girl given a female appearance of the external genitalia.

At age 1 year, diagnostic laparoscopy identified a uterus, bilateral fallopian tubes, atrophic left gonad, and right clinical ovotestis with suspicion of a vas deferens. Wide resection of these tissues, concomitant right inguinal hernia repair and lymph node biopsy, with genital reconstruction including clitoral reduction were performed.

The final pathology report confirmed a right testicle and epididymis with a focus of gonadoblastoma and adjacent segment of vas deferens. The left fallopian tube was identified with a streak gonad containing a scant amount of ovarian stroma, but no mature ovarian follicles. A focus of gonadoblastoma was also identified on the left. This confirmed the diagnosis of mixed gonadal dysgenesis rather than an ovotesticular DSD.

Post-operatively, patient's incision became erythematous, with copious amounts of clear fluid drainage. The fluid was negative for urine by creatinine level, and was consistent with a clinical lymphatic leak. It was treated conservatively with leg elevation, compression stockings, and fluid and protein replacement. She underwent exploration of groin 9 days postoperatively. A generalized lymphatic ooze was noted and controlled with clip placement.

Urinalysis showed a protein level of 300 mg/dl. Further studies obtained included a serum total protein of 5.1 g/dl (6.3 g/dl -8.2 g/dl), serum albumin of 1.5 g/dl (3.8 g/dl-5 g/dl), and normal serum creatinine level. Review of her past records determined that her blood pressure had been above the 95 percentile for her age and length on several occasions without associated edema. At this point, a consulting pediatric nephrologist (TRW) diagnosed Denys-Drash syndrome.

DNA analysis (Sheffield Molecular Genetics Laboratory, United Kingdom) showed a point mutation 1180C>T (cytosine to thymine at pair #1180) in exon 9 of the WT1 gene, which has been described in patients with the Denys-Drash syndrome.

The child was treated with an ACE inhibitor (Captopril), both to manage her blood pressure and in an effort to minimize ongoing renal scarring from heavy proteinuria.

She did well for the next year, but by 2 years of age, she had significant renal failure (creatinine 3.8 mg/dl), accompanied by anemia, hypertension, oliguria, and anasarca. Peritoneal dialysis was begun.

The child has tolerated dialysis well. Although serial renal ultrasounds have shown no evidence of the development of Wilms' tumor, bilateral nephrectomy is planned.

Discussion

In retrospect, this child likely had longstanding nephropathy. However, the gradual onset of her nephrotic syndrome, during a time in which she was growing, precluded clinical recognition in the absence of frank edema. It was only when postoperative incisional drainage developed that her nephrotic syndrome was recognized.

Although ovotesticular DSD has been associated with a karyotype of 46 XY, in our case, the absence of well-formed ovarian follicle and testicular tissue on the side of the streak confirmed mixed gonadal dysgenesis (MGD).[8-10] Interestingly, the karyotype in MGD is commonly 46, XX/45, XO.[10]

Mixed gonadal dysgenesis can be associated with Denys-Drash syndrome. This entity is characterized by progressive nephropathy and Wilms' tumor.[2-4] To date, there is one report describing the coexistence of nephritis, nephrotic syndrome, and nephroblastoma in association with genital anomalies.[11] In each of the eight cases described, a segment of Y chromosomal material was identified. Interestingly, the associated renal disorders have not been described in gonadal dysgenesis with karyotypes lacking the Y component (i.e. XO, XX).[11] Recent work has demonstrated a role for mutations in the developmentally expressed WT-1 gene in these disorders.[5,7,12] To our knowledge, no data exist as to the incidence of Denys-Drash syndrome in patients with ambiguous genitalia.

Blanchet et al described a 14-year-old phenotypic female who developed a gonadoblastoma after renal transplantation. Subsequent karyotype confirmed XY gonadal dysgenesis.[13] In a second report, renal disease was recognized at age 14, and ultimate renal failure at age 23.[14] A significant delay in the diagnosis of XY gonadal dysgenesis occurred in both of these patients of 2 and 9 years, respectively. Harkins and coworkers recommend that young women who have not developed secondary sex characteristics or have primary amenorrhea should be screened with FSH in cases of associated renal disease and a serum creatinine and urinalysis in patients with XY gonadal dysgenesis.[14]

To the best of our knowledge, there are no specific guidelines in the urologic literature as to what minimum work up is indicated in DSD states, excluding congenital adrenal hyperplasia. Guidelines for radiologic testing, including ultrasound, MRI, and genitogram, do exist.[15] Our patient's preoperative serum creatinine was 0.4 mg/dl, and her serum electrolytes were normal. She did not, however, have a urinalysis or serum albumin measurement preoperatively by the pediatrician. She did have borderline hypertension. Unfortunately, her disease was diagnosed only after a postoperative complication of a lymphatic leak has developed.

Although mixed gonadal dysgenesis is rare, the pediatric urologist should be familiar with its associated problems. In the era of outpatient surgery and cost efficiency, less preoperative metabolic testing is done, and common screening measures often are overlooked.

DNA sequencing of the WT-1 gene is a costly procedure, available only in a European reference laboratory. It would not be appropriate as a first line test. On the other hand, as our patient demonstrated, a simple measurement of serum creatinine is also insufficient. Renal failure in this condition may take years to evolve, and creatinine may not be elevated in infancy.

Since proteinuria will be present even in the absence of a frank nephrotic syndrome, however, urinalysis is a simple, inexpensive first line investigation. If any urine protein is detected, nephrology and clinical genetics evaluation for Denys-Drash syndrome is necessary. Establishing this diagnosis early allows for screening for the development of Wilms' tumor before it becomes advanced. □

References

1. New MI. An update of congenital adrenal hyperplasia. *Ann NY Acad Sci* 2004;1038:14-43.
2. Denys P, Malvaus P, Van Der Berghe H et al. Association d'un syndrome anatomo-pathologique de pseudohermaphrodisme masculine, d'une tumeur de Wilms', d'une nephropathie parenchymateuse et d'un mosaicisme XX/XY. *Arch Franc Pediatr* 1967;24:729-739.
3. Drash A, Sherman F, Hartmann W et al. A syndrome of pseudohermaphroditism, Wilms' tumor, hypertension and degenerative renal disease. *J Pediatr* 1970;76:585-593.
4. Mueller RF. The Denys-Drash syndrome. *J Med Genet* 1994;31:471-477.
5. Pelletier J, Bruening W, Kashtan CE et al. Germ line mutations in the Wilms' tumor suppressor gene are associated with abnormal urogenital development in Denys-Drash syndrome. *Cell* 1991;67:437-447.
6. Rudin C, Pritchard J, Fernando ON et al. Renal transplantation in the management of bilateral Wilms' tumor (BWT) and of Denys-Drash syndrome (DDS). *Nephrol Dial Transplant* 1998;13:1506-1510.
7. Schumacher V, Scharer K, Wuhl E et al. Spectrum of early onset nephrotic syndrome associated with WT-1 mis-sense mutations. *Kidney Int* 1998;53:1594-1600.
8. Krob G, Braun A, Kuhnle U. True hermaphroditism: geographical distribution, clinical findings, chromosomes and gonadal histology. *Eur J Pediatr* 1994;153:2-10.
9. Sohval ARE. 'Mixed' gonadal dysgenesis: a variety of hermaphroditism. *Am J Hum Genet* 1963;15:155-157.
10. Davidoff F, Federman DD. Mixed gonadal dysgenesis. *Pediatrics* 1973;52:725-742.
11. Gertner J, Kauschansky A, Giesker D et al. XY gonadal dysgenesis associated with the congenital nephrotic syndrome. *Obstet Gynecol* 1980;55:66-9S.
12. Grundy P, Coppes MJ, Haber D. Molecular genetics of Wilms' tumor. *Hematol Oncol Clin North Am* 1995;9:1201-1215.
13. Blanchet P, Daloze P, Lesage R et al. XY gonadal dysgenesis with gonadoblastoma discovered after kidney transplantation. *Am J Obstet Gynec* 1977;129:221-222.
14. Harkins PG, Haning RV, Shapiro SS. Renal failure with XY gonadal dysgenesis: report of the second case. *Obstet Gynec* 1980;56:751-752.
15. Aaronson IA, Cremin BJ. Clinical pediatric uroradiology. Edinburgh: Churchill Livingstone, 1984:385.