Denys-Drash Syndrome

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In 1967, Denys et al. described the triad of ambiguous genitalia, nephrotic syndrome and Wilms' tumor in an XX/XY mosaic(l). Three years later, Drash et al. described the triad in two patients and suggested that it may be a syndrome(2). Since then the syndrome has come to be known as the Drash syndrome or, more appropriately, as the Denys-Drash syndrome. More than 60 patients with this syndrome have been reported(3). We report on a child with this syndrome to highlight the issues that made the diagnosis difficult in our case.

Case Report

An 18-month-old child presented with a history of ambiguous genitalia noted at birth, and increasing abdominal distension for 1 month prior to presentation. The parents were non consanguineous and the antenatal and natal periods were uneventful. A sister had died at 25 days of age with a history of loose stools since birth.

At admission, the child had a weight of 5 kg (<5th centile) and length 72 cm (<5th centile). The blood pressure was 100/70 mm Hg (<90th centile). There was no hepatosplenomegaly. A large lump was palpable in the right lumbar region, which was ballotable and not crossing the midline. There was no ascites. The external genitalia were ambiguous with a stretched phallus length of 1.5 cm. Labioscrotal folds were present but no gonads were palpable. There was a single perineal urogenital opening. The uterus was not palpable on per rectal examination. The rest of the physical examination and development were normal.

On investigation, hemoglobin was 8.3 g/dl and TLC 10,800/mm^3. Blood urea was 30 mg/dl, creatinine 0.7 mg/dl, sodium 136 mmol/L and potasssium 3-2 mmol/L. Total serum proteins were 5.7 g/dl (albumin 2.7 and globulin 3.0), serum bilirubin was 0.4 mg/dl, SGOT 13 U/L, SGPT 12 U/L and alkaline phosphatase 191 U/L. Urinalysis showed 3+ proteinuria, 5-8 WBCs per high power field and no red cells or casts. Serum cortisol (midnight and morning) and 17 alpha-OH progesterone levels were in the normal range. Basal testosterone and DHEAS levels were in the low normal prepubertal range. The peripheral blood lymphocyte karyotype was 46, XY.

Bone age was 1 to 1.6 years. Chest X-ray was normal. Ultrasound of the abdomen showed a right suprarenal mass.

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No mullerian duct structures were seen in the pelvis. CT of the abdomen showed a homogeneous mass in the right suprarenal area with a few areas of low attenuation suggestive of necrosis *(Fig.* 1). The kidney was seen separately from the tumor mass but the anterior margin was not well defined. On the basis of these findings the mass was thought to be either a suprarenal or renal mass. A DMSA scan suggested that the tumor was of suprarenal origin.

During the hospital stay the child developed pedal edema and ascites. Proteinuria was in the nephrotic range as evidenced by a urinary albumin to creatine ratio of 5. Total serum proteins fell to 3.5 g/dl (albumin 1.3 and globulin 2.2). The child was taken up for exploratory laparotomy. At surgery, a large tumor was seen, measuring 20 x 15 cm in size, and arising from the right kidney. The mass was densely adherent to the right lobe of the liver which was thinned out. The tumor was infiltrating the retroperitoneum, gut and inferior vena cava. The right adrenal was normal, but compressed by the tumor. The left kidney was normal. The tumor was extremely friable and resection led to extensive bleeding. The child received multiple blood transfusions intra operatively and postoperatively, but died on the second postoperative day, of hemorrhagic shock. Histologic evaluation of the tumor mass was compatible with a diagnosis of Wilms' tumor. There were focal areas of renal mesangial hypercellularity (Fig. 2), although no evidence of mesangial sclerosis was seen.

Discussion

The major issue in our patient was the preoperative diagnosis of a possible suprarenal tumor, which is not a feature of Drash syndrome. It was only on laparotomy, when the tumor was seen to arise from the right kidney, that the correct diagnosis of Wilms' tumor was made and subsequently confirmed by histopathology. Thus, the diagnosis of Denys-Drash syndrome in our patient was necessarily retrospective.

The triad of intersex disorder, glornerulopathy and Wilms' tumor of the Denys-Drash syndrome presents a

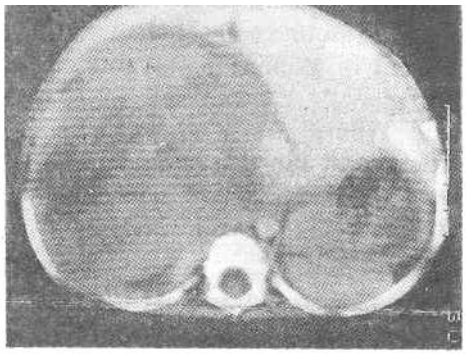

Fig. 1. Abdominal CT scan showing large mass in the right suprarenal area with a few areas of low attenuation suggestive of necrosis.

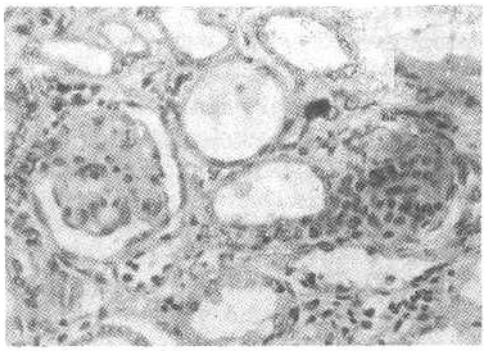

Fig. 2. Section through tumor mass with glomeruli showing mesangial hypercellularity (H & E × 1000).

serious problem, for which effective management is available, in the event of early diagnosis. Initially, the syndrome included only male patients with pseudohermaphroditism, glomerulopathy and Wilms' tumor. Subsequently, female patients with this triad were also described(3-5). The genital malformations vary considerably, the spectrum ranging from penoscrotal hypospadias with bilateral cryptorchidism to an enlarged clitoris with labia that are almost fused and a urogenital sinus, in patients with a 46, XY karyotype. However, most patients with a 46, XX karyotype (6 out of 7 reported cases) have been noted to have normal external genitalia (6). The internal genitalia can also be affected; the abnormality varying from a small atrophic vagina and uterus to the presence of streak ovaries or dysgenetic testes only.

The nephropathy in this syndrome is characterized by onset of proteinuria between birth to two years of age, although it may develop as late as 6 to 14 years of age (7). As many as 50% of children present with proteinuria before one year of age. Proteinuria evolves into nephrotic syndrome and rapidly progresses to end stage renal failure (ESRF) (3). Varying degrees of focal and diffuse mesangial sclerosis are the most consistent histopathological findings in the kidneys (4).

A 50% risk of developing Wilms' tumor has been reported in this syndrome(7). The mean age at diagnosis of Wilms' tumor is 1.6 years(3), which is earlier than the age at diagnosis for isolated Wilms' tumor as reported by the National Wilms' Tumor Study(8). The incidence of bilateral Wilms' tumor is also notably high in patients with this syndrome(3). There is also a significantly higher rate of intralobar nephrogenic rests in patients with this syndrome indicating an early defect in embryogenesis(9). Mutations of the Wilms' tumor suppressor gene (WTI), located on the short arm of chromosome 11 (Ilpl3), have been documented in this syndrome(l0). The WTI gene plays a vital role in both genital and renal development. The WTI mutations are clustered in the zinc finger encoding exons, and thus interfere with the binding of the normal WTI gene products to their normal target DNA(11).

Gonadal tissue in these patients has a high likelihood of becoming malignant, and gonadoblastomas have been described in several patients(6,9,12).

It is important to consider the diagnosis of Denys-Drash syndrome in any patient with unexplained nephropathy, particularly young phenotypic girls and children with ambiguous genitalia, or those presenting with an early Wilms' tumor. In patients with ambiguous genitalia and renal disease a close follow-up should be maintained, with regular renal ultrasound scans, to look for development of Wilms' tumor and gonadal malignancy. Conversely, in patients with Wilms' tumor and intersex disorder, renal function should be serially assessed to document development of proteinuria and renal insufficiency.

Most deaths in patients with the Denys-Drash syndrome are due to ESRF. The approach to therapy should be vigorous and optimistic, with bilateral nephrectomies, even before ESRF develops, because of the risk of early development of Wilms' tumor. Because of the

high rate of malignancy in the dysgenetic gonads found in these patients, gonadal biopsises should be carried out for complete diagnosis, and gonadectomy performed if indicated. Better dialysis and transplantation programs for young children constitute the major factor in improved prognosis.

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