Denys-Drash Syndrome - A Case Report.

**Corresponding Author:**
Dr. A Shrikiran,
Professor, Pediatrics, KMC Manipal - India

**Submitting Author:**
Dr. A Shrikiran,
Professor, Pediatrics, KMC Manipal - India

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Denys-Drash Syndrome - A Case Report.

Author(s): Shrikiran A, Suneel M

Case Report

A 6 month old girl first presented to us in September 2002 with anasarca and oliguria of one month duration. She was the third child in her family. Two elder sisters were healthy. Birth history and development till onset of illness were normal. On examination, her weight was 7 kg and length 64 cm. She also had hypertension and ascites. Investigations: Blood biochemistry: Blood urea 26mg/DL (9.28 mmol/L), S.creatinine 0.4mg/DL (70.7 mmol/L), S.sodium 124mmol/L, S.potassium 2.4 mmol/L, serum albumin – 1.3g/DL (13 g/L), total serum protein – 3.3g/DL (33 g/L), C3 – 54mg/DL (540 mg/L) and 24-hour urine protein of 69 mg/sq. m²/hr. VDRL test, ELISA tests for herpes simplex, rubella, HIV and for toxoplasma were negative. But ELISA test for IgM, cytomegalovirus was positive. Opthalmological evaluation revealed diffuse pigment mottling of both the fundi suggesting salt and pepper pattern of retinopathy of CMV retinitis. Mothers blood ELISA for CMV was negative. The child was diagnosed with infantile nephrotic syndrome with CMV retinitis. She was started on Captopril and Nifedipine. I.V. Ganciclovir was administered for four weeks. At the end of this period, CMV IgM was negative and oral ganciclovir could not be started due to non-availability of the drug. Her edema gradually resolved. Renal biopsy was deferred due to poor general condition of the child and non-willingness of the parents. Steroids were not tried due to its known inefficacy in infantile nephrotic syndrome with CMV retinitis. The renal biopsy done, had adequate number of glomeruli, with majority of them showing varying degrees of sclerosis and an occasional glomerulus showing mild mesangial hypercellularity. The tubules are moderately atrophic with hyaline casts. The interstitium showed marked fibrosis with a moderately dense infiltrate of lymphocytes, the features suggestive of an end stage renal disease with pyelonephritic changes. Direct immunofluorescence with IgG, IgA, IgM and C3 showed non specific immune deposits.

At 3 years of age she developed a mass on the left side of the abdomen in lumbar region. On examination, it was firm and measured 7x 7 cm in size. CT scan study of the abdomen revealed heterogeneously enhancing soft tissue density lesion, measuring 9x 7.3 cm arising from the anterior renal parenchyma of the left kidney. Another similar mass of size 3x 2.2 cm was seen located in the anterior aspect of the interpolar region of the right kidney. Radiological findings favoured the diagnosis of bilateral Wilms' tumour (Fig 1 & 2). Fine needle aspiration (FNA) from both the renal masses were performed under ultrasound guidance using separate needle and syringe and the smears were fixed in absolute alcohol, stained with Papanicolaou stain and separately analysed. The smears from both the right and left renal masses were cellular and showed diffuse sheets and clusters of blastemal cells having round to oval nucleus with fine chromatin, indistinct nucleolus and scanty basophilic cytoplasm. An occasional mitosis was seen (1/10hpf). At places rosette like arrangement of blastemal cells with no central fibrillary material, suggestive of epithelial differentiation was observed. A few spindle shaped cells admixed with blastemal cells was noted (Fig 3). The cytologic features were diagnostic of classic Wilms’ tumor involving both the kidneys. Karyotyping revealed a normal 46, XX genotype. Renal function progressively deteriorated with increasing S.creatinine level. Child was started on combination chemotherapy with Vincristine, Actinomycin D and Doxorubicin. However the response was poor without significant decrease in the mass size and renal failure progressed further. Child finally succumbed to the illness with in 6 months of detection of the tumour.

Discussion

Early onset nephrotic syndrome is called congenital, if the onset is prior to 3 months of age and infantile if symptoms appear later in infancy(3). The two main types of early onset nephrotic syndrome are the Finnish type and Diffuse Mesangial Sclerosis. Additionally, Syphilis and other perinatal infections can also be associated with congenital nephrotic syndrome.
The Denys-Drash syndrome (DDS) is a triad of congenital nephropathy, Wilms' tumour and intersex disorders, first described by Denys et al in 1967 and Drash et al in 1970. Nephropathy is a constant feature of DDS. Renal dysfunction usually progresses to end stage renal disease by the age of three years. In incomplete forms of the syndrome, nephropathy exists either with Wilms' tumor or with intersex disorder. Genital abnormalities are frequently seen in patients with 46 XY karyotype, while those with 46 XX show less or no genital abnormality(4). This subgroup of DDS children subsequently have normal development with normal puberty if they survive the renal disease and Wilms tumour. All cases of suspected Denys-Drash syndrome should thus have a karyotyping and USG abdomen for complete evaluation. Ideally, molecular studies should also be done for WT1 gene mutation at 11p13 locus. Most, but not all patients with Denys Drash Syndrome develop Wilms' tumour. The median age FNA cytology is a very accurate technique for preoperative diagnosis of Wilms’ tumour, especially when the aspiration is performed under ultrasound guidance(6). A posterolateral approach prevents tumour spillage into the peritoneum(7). The differential diagnosis on FNA cytology includes neuroblastoma, which contain fibrillary material at the centre of the rosettes, non-Hodgkins lymphoma which lack epithelial differentiation and contain lymphoid globules in the background. Other tumors like rhabdomyosarcoma, immature teratoma, clear cell sarcoma of the kidney and the rhabdoid tumor of the kidney are all monomorphic and lack the bimodal blastemal and stromal cells seen in classic Wilms' tumor(6). Congenital nephrotic syndrome is often steroid resistant and frequently associated with hypertension. The common age of onset of nephrotic syndrome is from 2 weeks to 18 months and progresses to renal failure by 3-4 years of life(2). The condition does not recur after renal transplant.

The commonest mode of presentation is an incidentally detected abdominal mass, as it is in our case. Our case presented with bilateral Wilms' tumour, which is Stage V involvement. Chest X-ray did not show lung involvement. Surgical extirpation is the primary treatment for Wilms tumour. However, it is often beneficial to use preoperative chemotherapy to shrink the tumour and facilitate resection. Adjuvant chemotherapy is with Actinomycin D, Vincristine and Doxorubicin. In patients with bilateral tumours (as in our case) or single kidney, conservation of nephrons is a priority. Bilateral resection with preservation of renal function is impossible in children with end stage renal disease, where it may be necessary to remove both kidneys, with renal transplantation after a period of dialysis. Our case probably required this line of management. Bilateral nephrectomy followed by renal transplantation is the treatment of choice for this condition, even prior to the onset of associated Wilms tumour.

Our case had infantile nephrotic syndrome at presentation. As she also had ELISA for CMV positive with retinitis, which is a known cause for congenital/infantile nephrotic syndrome, she was treated accordingly. Also that as no genital abnormality was present, complete Denys-Drash syndrome was not suspected. However incomplete form of the same may exist with out genital abnormality. Hence ideally, these patients need molecular studies for detecting WT1 gene mutation at 11p13 locus to diagnose in advance i.e., before Wilms tumour develop. Confirmation of CMV infection in the baby by PCR or viral culture, would have confirmed the diagnosis could not be done in this case.

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