

Denys-Drash syndrome

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Abstract

Denys-Drash syndrome is characterized by the association of diffuse mesangial sclerosis (DMS), male pseudohermaphroditism with a 46,XY karyotype, and nephroblastoma. Proteinuria develops after birth and is responsible for a nephrotic syndrome. Progression to renal failure is constant within 1 to 4 years. Nephrotic syndrome does not recur after kidney transplantation. DMS may be isolated or may occur in association with male pseudohermaphroditism and/or nephroblastoma. The WT1 gene encodes a zinc-finger protein, which is probably a transcription factor involved in renal and genital development. Constitutive mutations in the WT1 gene, most of which are located in exons 8 and 9, have been described in the majority of patients with Denys-Drash syndrome. Mutations are dominant, as patients are usually heterozygous.

Keyword

Denys-Drash syndrome, diffuse mesangial sclerosis (DMS), male pseudohermaphroditism, nephroblastoma, WT1 gene.

Disease name and synonyms

- Denys-Drash syndrome
- Drash syndrome
- Wilm's tumor and pseudohermaphroditism
- Nephropathy, Wilm's tumor and genital anomalies

Diagnosis Criteria/ Definition

Denys *et al.* and Drash *et al.* were the first to report the triad of progressive renal disease, male pseudohermaphroditism and Wilms' tumor [1,2]. All of the patients were infants with severe proteinuria progressing rapidly to renal failure. Incomplete forms of the syndrome were

described and the glomerulopathy was identified as diffuse mesangial sclerosis (DMS) [3].

During the early stages, the glomerular lesions are characterized by a high amount of fibrils in the mesangial matrix without mesangial cell proliferation [4-6]. The capillary walls are lined with hypertrophied podocytes. The fully developed lesion consists of thickened glomerular basement membranes associated with massive enlargement of mesangial areas, leading to the reduction of the capillary lumens. Mesangial sclerosis eventually contracts the

glomerular tuft into a sclerotic mass within a dilated urinary space. There is usually a corticomedullary gradient of involvement, with the most central glomeruli being less affected. Tubules are severely damaged, especially in the deeper cortex, where they are markedly dilated and often contain hyaline casts.

Incidence

More than 60 cases of Denys-Drash syndrome have been reported to date [1-3,7,8]. The Denys-Drash syndrome is usually sporadic, although occurrence in two kindreds has been reported.

Clinical description

DMS is a constant feature of the Denys-Drash syndrome. It is associated with the two other components of the triad in the complete form, but with only one of the two in the incomplete forms.

The clinical course of the nephropathy is the same as that described for isolated DMS. Proteinuria is usually discovered within the first months of life, sometimes at birth. Progression to end-stage of renal failure before the age of 4 years is the rule. There is no recurrence of nephrotic syndrome after renal transplantation. Wilms' tumor may be the first clinical manifestation of the syndrome. Thus, careful renal ultrasonography should be performed, looking for nephroblastoma, in any patient found to have DMS. The tumor may be unilateral or bilateral and is associated in a few cases with nodules of nephroblastomatosis [5,9].

Male pseudohermaphroditism, characterized by ambiguous genitalia or female phenotype with dysgenetic testis or streaked gonads, is observed in all 46,XY patients. In contrast, all 46,XX children appeared to have a normal female phenotype, with normal ovaries, when the information was available. The finding of a normal male phenotype seems to exclude the diagnosis of Denys-Drash syndrome.

Treatment

The nephrotic syndrome is resistant to corticosteroids and immunosuppressive drugs. The degree of proteinuria is typically less severe than in congenital nephrotic syndrome of the Finnish type and specific supplemental therapy is usually not required.

Treatment is supportive and consists of maintenance of electrolyte and water balances and adequate nutrition, prevention and treatment of infectious complications, and management of renal failure. Bilateral nephrectomy has been considered at the time of transplantation because of the theoretical risk of developing Wilms' tumor. This issue remains unresolved,

although Habib found no Wilms' tumor in the kidneys of 14 children with renal failure [16]. The disease does not recur in the graft.

Etiology

Constitutional mutations occur in the Wilms' tumor predisposing gene, *WT1* [9] even though Denys-Drash syndrome is usually sporadic.

Wilms' tumor is an embryonic kidney tumor thought to arise from aberrant mesenchymal stem-cell differentiation secondary to the loss of a tumor-suppressor gene or genes [10,11]. The *WT1* gene is located at chromosome 11p13; it appears to encode a zinc-finger protein, which is probably a transcription factor [12-15]. *WT1* is also expressed in the gonads, suggesting that the genital abnormalities in the Denys-Drash syndrome may result from pleiotropic effects of mutations in the *WT1* gene itself. This hypothesis was first confirmed in a report which identified constitutional heterozygous mutations within the *WT1* gene in some individuals with the Denys-Drash syndrome [16].

Subsequently, *WT1* mutations have been found in most patients with this syndrome. Most abnormalities are missense changes either in exon 9, which encodes for zinc finger 3 (with a mutational hot spot at an arginine residue thought to interact with the consensus DNA sequence), or in exon 8, which encodes zinc finger 2 [17].

Genetic counseling

In most children, constitutive *WT1* mutations are found and the risk for another sibling to be affected is extremely low.

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