Clinical Kidney Journal, 2019, vol. 12, no. 6, 836–839

doi: 10.1093/ckj/sfz022
Advance Access Publication Date: 16 March 2019
Original Article

ORIGINAL ARTICLE

Long-term outcome in a case series of Denys–Drash syndrome

Neus Roca [1], Marina Muñoz[2], Alejandro Cruz[2], Ramon Vilalta[2], Enrique Lara[3] and Gema Ariceta[4]

[1]Pediatric Nephrology, Consorci Hospitalari de Vic Ringgold Standard Institution, Francesc Pla el Vigata n°1, Vic 08500, Spain, [2]Pediatric Nephrology, Hospital Vall d'Hebron Ringgold Standard Institution, Barcelona, Catalunya, Spain, [3]Pediatric Nephrology, Hospital Vall d'Hebron, Barcelona, Spain and [4]Pediatric Nephrology, Hospital Universitario Vall d'Hebron, Passeig de la Vall d'Hebron, Barcelona, Spain

Correspondence and offprint requests to: Neus Roca; E-mail: n.roca.saladrigues@gmail.com; Twitter handle: @NeusRoca8

ABSTRACT

Background. Denys–Drash syndrome (DDS) is a rare disease caused by mutations in exons 8 and 9 of the *WT1* gene. It is characterized by the association of early onset steroid-resistant nephrotic syndrome (SRNS), Wilms' tumour and, in some patients, intersex disorders, with increasing risk of gonadoblastoma. There are few published data concerning the long-term outcome of patients with DDS. The aim of this study was to report our experience.

Methods. Data were collected from five children (three boys) with confirmed DDS diagnosed from 1996 to 2017. The mean follow-up of these patients was 16 years.

Results. The patients presented with SRNS and diffuse mesangial sclerosis at renal biopsy. All patients were hypertensive and progressed to end-stage kidney disease, initiating dialysis at a mean age of 28 months. Three patients developed Wilms' tumour 9 months after the SRNS was identified, which was treated by nephrectomy and chemotherapy. All five patients received kidney transplantation. SRNS did not recur after transplantation in any of the patients and graft survival was similar to that of other kidney transplant recipients in our programme. All three boys had ambiguous genitalia and cryptorchidism but a confirmed male karyotype (46, XY). One girl presented with gonadal agenesis, whereas the other one had normal female ovarian tissue and external genitalia. Both girls had a female karyotype (46, XX). Gonadoblastoma was not observed at any case.

Conclusions. Early DDS recognition in patients with SRNS is crucial due to its low prevalence, the specific treatment approach required and early detection of Wilms' tumour. Few data are available regarding long-term outcomes.

Keywords: Denys–Drash, intersex disorders, steroid resistant nephrotic syndrome, Wilms' tumour, *WT1*

Received: 15.11.2018. Editorial decision: 31.1.2019

INTRODUCTION

Denys–Drash syndrome (DDS) (Online Mendelian Inheritance in Man database identifier 194080) is a rare genetic cause of steroid-resistant nephrotic syndrome (SRNS) during the first year of life [1]. Its prevalence is unknown but is estimated to be <1/10 000. The complete form of DDS is characterized by nephropathy, Wilms' tumour and intersex disorders. In addition, affected patients have an increased risk of developing gonadoblastoma. Incomplete variants have been described with nephropathy as a constant feature [2], which represents a diagnostic challenge.

DDS is caused by mutations in the Wilms' tumour suppressor gene (*WT1*) on chromosome band 11p13. The *WT1* gene encodes a transcription factor that is involved in the development of the kidneys and gonads. Several mutations have been described. The most frequent mutations consist of heterozygous germline missense changes in exons 8 and 9 [3], which encode zing fingers 2 and 3, respectively. Such mutations alter the binding of the WT1 protein to DNA [4]. DDS is inherited as an autosomal dominant trait. Most cases of DDS result from *de novo* mutations in the gene, with no previous familial history of the disorder.

The main histological pattern of DDS is mesangial sclerosis [5]. Nephropathy presents as an early SRNS and immunosuppressive drug–resistant nephrotic syndrome that progresses to end-stage kidney disease (ESKD) before 2–3 years of age, associated with severe hypertension. Furthermore, affected patients have a high risk of developing Wilms' tumour, which may constitute part of the picture of DDS onset or occur later. Therefore it is important to screen all newly diagnosed DDS patients via abdominal computed tomography (CT) scanning and continue close follow-up afterwards. The median age of Wilms' tumour presentation in DDS patients is 12.5 months, which is younger than in isolated Wilms' tumour forms. Total nephrectomy is recommended at the time of kidney transplantation because the risk of developing Wilms' tumour in any residual renal tissue is very high [6].

WT1 is also involved in other diseases, such as Frasier syndrome and isolated nephrotic syndrome, which should also be considered at the time of DDS diagnosis [4] (see Table 1). According to the PodoNet registry, the prevalence of *WT1* mutations in sporadic SRNS patients is ∼6% and, of affected patients, 28% present with an isolated SRNS clinical picture [7].

Frasier syndrome is characterized by the association of nephrotic syndrome, normal female genitalia with streak gonads, an XY karyotype and increased risk of developing gonadoblastoma (37–47%) [8]. Such a high risk supports the performance of prophylactic gonadectomy at the time of Frasier syndrome diagnosis. Focal and segmental glomerular sclerosis is the characteristic renal histological pattern. The progression to ESKD is slower than in DDS, occurring in around the third decade of life [7, 8].

The aim of this study was to describe our experience and long-term outcome of patients with DDS.

MATERIALS AND METHODS

We performed a retrospective analysis of all paediatric patients diagnosed with DDS in our paediatric nephrology service at a tertiary hospital between 1996 and 2017. Epidemiological and clinical data of those patients from diagnosis through 2018 were collected to study long-term outcomes. The mean follow-up of these patients was 16 years.

RESULTS

Five patients diagnosed with DDS during the period of study were identified. There were three males and two females, with an average age of 16 years (range 3–34) at the time of the study. Patient medical records were reviewed (see Table 2). Three cases presented the complete DDS triad, whereas two exhibited incomplete forms; one suffered renal disease and genital abnormalities and the other had nephropathy and Wilms' tumour. The disease manifested at a mean age of 11 months as SRNS in four children and as Wilms' tumour in the fifth child. Renal biopsy demonstrated diffuse mesangial sclerosis in all cases.

Further molecular analyses confirmed DDS in four patients who presented with exon 9 *WT1* mutations (see Table 2). Genetic testing was not available in the oldest patient, whose diagnosis was based on the complete DDS triad.

After specific diagnosis, every patient was screened for Wilms' tumour by abdominal ultrasound and CT. In one case, CT identified a single Wilms' tumour that was not observed by ultrasound. Two patients developed Wilms' tumour 9 months after the diagnosis of DDS (at 15 and 18 months of age). All Wilms' tumour cases underwent unilateral nephrectomy and received chemotherapy and, after progressing to ESKD, contralateral nephrectomy (36 months mean time from the first nephrectomy) to prevent the very high risk of tumour recurrence, as described in Auber *et al.* [9]. No histologic signs of Wilms' tumour were identified. The patient without Wilms' tumour also underwent bilateral nephrectomy after progressing to ESKD as a prophylactic treatment due to the high risk of malignancy in DDS.

Table 1. Comparison of the characteristics of DDS, Frasier syndrome and isolated kidney disease

Clinical characteristics	DDS	Frasier syndrome	Isolated kidney disease
WT1 mutations	Most common missense mutations of exons 8 and 9	Mutations in donor splice site intron 9	Not present in all patients
SRNS	Early onset (<1 year of life)	Later onset (2–6 years of life)	Early onset (<2 years of life)
Renal histological pattern	Diffuse mesangial sclerosis	Focal segmental glomerulosclerosis	Diffuse mesangial sclerosis
End-stage renal disease	Early childhood (<3 years of life)	Later (second or third decade of life)	Early childhood
Intersex disorders	Male pseudohermaphroditism (ambiguous genitalia or female phenotype with streak gonads)	Complete XY gonadal dysgenesis with female phenotype	No
Wilms' tumour	High risk (early presentation)	Low risk	No
Gonadoblastoma	Low risk	High risk	No

Table 2. Clinical data of DDS patients

Patient	Gender phenotype	Age at diagnosis	Clinical presentation	*WT1* mutation	Age at Wilms' tumour (months)	Genitalia	Age at ESKD (months)	Initial renal replacement therapy	Age at renal transplant (years)	Follow-up (years)
1	F	36 months	WT	*WT1* exon 9 (1215T>A)	36	Ovarian atrophy	36	HD	4	18
2	F	6 months	NS	*WT1* exon 9 (R394W)	17	Normal	36	PD	4	8
3	M	15 days	NS	*WT1* exon 9 (1335T>A)	–	Bilateral cryptorchidism and hypospadias	8	HD	1	19
4	M	13 months	WT and NS	NA	13	Unilateral cryptorchidism and micropenis	60	HD	6	33
5	M	21 days	NS	*WT1* exon 9 (394A>G)	16	Bilateral cryptorchidism	3	PD	3	2

F, female; M, male; WT, Wilms' tumour; NS, nephrotic syndrome; NA, not available; HD, haemodialysis; PD, peritoneal dialysis.

During follow-up, all patients progressed to ESKD associated with severe hypertension. Renal replacement therapy was initiated at a mean age of 28 months (range 8–60). Two patients were treated with peritoneal dialysis and three with haemodialysis and all received a kidney transplant at a mean age of 3.5 years (range 1–6). SRNS did not relapse afterwards. Two patients lost their grafts shortly after transplantation due to acute graft thrombosis and early acute rejection and later received a second kidney transplant. In the long-term, two patients lost their grafts after 9 years because of chronic allograft dysfunction. At the time of the study, one patient was active on the transplant waiting list, whereas the remaining patients maintained functional transplants. Regular immunosuppressive treatment was administered initially, but more contemporary cases received tacrolimus in combination with mammalian target of rapamycin (mTOR) inhibitors. The mean time between Wilms' tumour diagnosis and the beginning of immunosuppressive therapy was 28 months (range 12–53). One patient developed hepatitis C infection post-transplant, but the others did not develop any severe infections or malignant diseases.

Regarding endocrine disorders, both females had normal external genitalia, but one presented with ovarian atrophy. Elective ovarian biopsy confirmed normal ovarian tissue in the other girl. In contrast, all three boys presented with cryptorchidism at birth and hypospadias of variable severity. Karyotype analysis confirmed female and male gender assignment based on external genitalia. Native gonads were preserved and no patients developed gonadoblastoma.

DISCUSSION

Most children with SRNS, especially those with early onset during the first year of life, present inherited podocytopathies. These can manifest as an isolated glomerular disease or as a syndromic disorder with extrarenal involvement. The most prevalent genes causing early onset SRNS are *NPHS1*, *NPHS2*, *WT1*, *PLCA1* and *LAMB2*. It is crucial that genetic nephrotic syndrome types are identified, since disease onset, management and prognosis of such patients differs from that of those with non-inherited SRNS. Genetic diagnosis is currently based on next-generation sequencing panels, which have replaced individual Sanger sequencing and allow the detection of pathogenic variants even in the absence of suggestive phenotypes [10].

The initial presentation of DDS is variable. Proteinuria is usually discovered within the first months of life, but Wilms' tumour can also be the first manifestation or can appear during follow-up. In this case series, patients presented with SRNS; two of the patients presented with incomplete forms of DDS (isolated glomerulopathy associated with either Wilms' tumour or genital abnormalities), as previously described [4].

As all patients had *WT1* mutations in the same exon, we cannot make any genotype/phenotype correlations.

In our experience, graft outcomes in DDS patients do not differ from the general group of paediatric kidney transplant patients in our programme. We did not see any recurrence of nephrotic syndrome, as previously published [6]. We support the use of mTOR inhibitors in DDS patients because of their ability to prevent tissue proliferation [11, 12].

We followed the recommendation of performing total kidney nephrectomy at the time of ESKD in patients with DDS to avoid Wilms' tumour development, particularly in patients who would receive immunosuppression. Therefore kidney transplantation should be delayed until nephrectomy [9, 13] and it has been

recommended that children with Wilms' tumour have a 1- to 2-year period free of chemotherapy before transplantation [6].

The incidence of gonadoblastoma in DDS patients is 4% [14], which is considerably lower than that of Frasier syndrome (37–46%) [9]. However, any patient with dysgenetic gonads carrying the Y chromosome has an increased risk of developing germ cell tumours such as gonadoblastoma [13]. As recommended, karyotype analysis and a biopsy were performed to determinate the best therapeutic approach for each case. Prophylactic gonadectomy needs to be considered in patients with complete XY gonadal dysgenesis or partial non-scrotal dysgenetic gonads that cannot be repositioned [13]. None of our patients suffered gonadoblastoma.

In conclusion, identifying DDS is crucial for early diagnosis and proper follow-up. All children presenting with nephrotic syndrome during the first year of life and those with SRNS with either Wilms' tumour or genital abnormalities should be screened for mutations in *WT1*. Therapeutic approaches and the monitoring of Wilms' tumour and gonadoblastoma need to be considered on an individual basis.

CONFLICT OF INTEREST STATEMENT

Dr. Ariceta reports personal fees from Alexion Pharmaceuticals, personal fees from Orphan Europe, personal fees from Chiesi, personal fees from Kyowa Kirim, outside the submitted work. The other authors declared no conflict of interest.

REFERENCES

1. Denys P, Malvaux P, Van Den Berghe H. Association of an anatomo-pathological syndrome of male pseudohermaphroditism, Wilms' tumor, parenchymatous nephropathy and XX/XY mosaicism. *Arch Fr Pediatr* 1967; 24: 729–739
2. Yang Y, Zhao F, Tu X *et al*. Mutations in WT1 in boys with sporadic isolated steroid-resistant nephrotic syndrome. *Genet Mol Res* 2016; 15: 15017559
3. Dome J, Huff V. Wilms tumor predisposition. In: Adam MP, Ardinger HH, Pagon RA, et al. (eds). *GeneReviews* Seattle: University of Washington, 2016
4. Niaudet P, Gubler MC, WT1 and glomerular diseases. *Pediatr Nephrol* 2006; 21: 1653–1660
5. Nso Roca AP, Peña A, Benito M *et al*. Evolutive study of children with diffuse mesangial sclerosis. *Pediatr Nephrol* 2009; 24: 1013–1019
6. Kist-van Holthe JE, Ho PL, Stablein D *et al*. Outcome of renal transplantation for Wilms' tumor and Denys-Drash syndrome: a report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatr Transplant* 2006; 9: 305–310
7. Lipska BS, Ranchin B, Iatropoulos P *et al*. Genotype–phenotype associations in WT1 glomerulopathy. *Kidney Int* 2014; 85: 1169–1178
8. Sinha A, Sharma S, Gulati A *et al*. Frasier syndrome: early gonadoblastoma and cyclosporine responsiveness. *Pediatr Nephrol* 2010; 25: 2171–2174
9. Auber F, Lortat-Jacob S, Sarnacki S *et al*. Surgical management and genotype/phenotype correlations in WT1 gene-related diseases (Drash, Frasier syndromes). *J Pediatr Surg* 2003; 38: 124–129
10. Ha TS. Genetics of hereditary nephrotic syndrome: a clinical review. *Korean J Pediatr* 2017; 60: 55–63
11. Hellström VC, Enström Y, von Zur-Mühlen B *et al*. Malignancies in transplanted patients: multidisciplinary evaluation and switch to mTOR inhibitors after kidney transplantation – experiences from a prospective, clinical, observational study. *Acta Oncol* 2016; 55: 774–781
12. Pape L, Ahlenstiel T. mTOR inhibitors in pediatric kidney transplantation. *Pediatr Nephrol* 2014; 29: 1119–1129
13. McCann-Crosby B, Mansouri R, Dietrich JE *et al*. State of the art review in gonadal dysgenesis: challenges in diagnosis and management. *Int J Pediatr Endocrinol* 2014; 1: 4
14. Mueller RF. The Denys-Drash syndrome. *J Med Genet* 1994; 31: 471–477