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Refractory Hypertension in Infantile-Onset Denys-Drash Syndrome

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Denys-Drash syndrome is characterized by progressive nephropathy, gonadal dysgenesis, and Wilms tumor caused by a *WT1* gene mutation. Infants with Denys-Drash syndrome frequently experience severe hypertension, but detailed clinical manifestations have yet to be clarified. Cases of infantile-onset Denys-Drash syndrome with severe hypertension at our hospital were retrospectively analyzed and the pathogenesis of hypertension was investigated. Six infants who received the diagnosis of Denys-Drash syndrome at the median age of 10 days (range: 2-182 days) were enrolled. Five infants had the complication of severe hypertension within a few days of diagnosis. All the patients showed rapid progression to end-stage renal disease and urgently required dialysis due to anuria/oliguria and hypervolemia with a median duration of 7.5 days (range: 0-17 days) on the day after diagnosis. Even under dialysis, all the patients continued to need antihypertensive treatment. Five patients underwent a preventive nephrectomy for Wilms tumor, and one patient underwent a nephrectomy due to progression to Wilms tumor. Two patients developed hypotension after a nephrectomy. The main causes of hypertension were hypervolemia in the predialysis stage, renin-associated hypertension in the dialysis stage, and multiple factors, including increased plasma catecholamine-associated hypertension in the postnephrectomy dialysis stage. At last the follow-up after bilateral nephrectomy, four of the five patients required antihypertensive treatment. Not all the patients showed target organ complications caused by hypertension. Severe hypertension is a common complication of infantile-onset Denys-Drash syndrome. The possibility of hypotension after nephrectomy should be considered in patients with Denys-Drash syndrome.

Keywords: Denys-Drash syndrome; hypertension; hypotension after nephrectomy; renin; *WT1*
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Introduction

Denys-Drash syndrome (DDS, MIM#194080) is a rare disease which comprises progressive nephropathy, gonadal dysgenesis, and Wilms tumor caused by a *WT1* gene mutation (Niaudet and Gubler 2006). *WT1* is a zinc-finger DNA transcription gene on chromosome band 11p13, which encodes a protein involved in kidney and gonad development. The nephropathy in DDS generally develops between the first months of life and 2 years of age and progresses to end-stage renal disease (ESRD) before 4 years of age (Mueller 1994; Niaudet and Gubler 2006). In particular, neonatal-onset DDS rapidly progresses to ESRD; our previous study reported the median of six days from onset to ESRD progression (Nishi et al. 2019). Diffuse mesangial sclerosis and immature tissue, including glomeruli and tubules, in the renal pathological findings of neonatal-onset DDS may be related to the rapid progression to ESRD (Nishi et al. 2019). Although renal failure is the most common cause of death in DDS, the prognosis is not necessarily

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bad if appropriate renal replacement therapy is performed (Nishi et al. 2019). A unilateral or bilateral Wilms tumor develops in 74% of DDS cases, the average age at presentation being 1.65 years (Mueller 1994). A bilateral nephrectomy for patients with ESRD is recommended to reduce the risk of Wilms tumor development. Ideally, renal transplantation is performed in infancy or early childhood (Mueller 1994).

Hypertension in DDS is life-threatening and sometimes difficult to manage (Davies et al. 1999; Niaudet and Gubler 2006). Hypertension in DDS is presumably associated with increased plasma renin activity (Steege et al. 2008). Moreover, it has been reported that a patient with DDS develops refractory postnephrectomy hypotension postulated to be secondary to the abrupt loss of plasma renin activity (PRA) (Hassinger and Garimella 2013). Nevertheless, the detailed clinical manifestations of patients with DDS with hypertension have yet to be clarified. Because the most common causes of death among infants on peritoneal dialysis are cardiac failure and infection, strict control of hypertension is important to improve outcomes (Sanderson et al. 2019). We therefore investigated herein the detailed clinical characteristics of hypertension and postnephrectomy hypotension in patients with infantile-onset DDS at our center.

Materials and Methods

Participants and data collection

Hypertension diagnosed between July 2013 and June 2019 in patients with infantile-onset DDS at the National Center for Child Health and Development was retrospectively investigated. Patients with DDS who developed nephropathy during infancy were included. For each patient, the following data were collected from the medical records: patient characteristics, clinical manifestations, laboratory data, details of hypertensive and hypotensive events, and the antihypertensive treatments administered.

Genetic analysis

WT1 gene sequencing was conducted using either a next generation sequencer or Sanger's sequencing. Genomic DNA was extracted and purified from peripheral leukocytes using a DNA isolation kit (Takara, Ohtsu, Japan). For next generation sequencer analysis, a custom panel was designed for targeted sequences, including the WT1 gene. Next generation sequencer samples were prepared using a HaloPlex Target Enrichment System Kit (Agilent Technologies, Santa Clara, CA, USA) to capture genes in accordance with the manufacturer's instructions. Amplified target libraries were sequenced using MiSeq (Illumina, San Diego, CA, USA) and analyzed with SureCall (v.3.0; Agilent Technologies). The variants detected were confirmed by Sanger sequencing, for which exons of *WT1* were amplified by polymerase chain reaction. The primer design was based on previously published information about intron-exon boundaries (Jeanpierre et al. 1998; Boute et al. 2000). Polymerase chain reaction products were purified with a QIA Quick polymerase chain reaction Purification Kit (Qiagen, Hilden, Germany). The purified product was cycle-sequenced with Big-Dye Terminators (Applied Biosystems, Foster City, CA, USA). The cycle sequence product was then analyzed with an automated sequencer (ABI Prism 310 Genetic Analyzer; Applied Biosystems) (Sako et al. 2005).

Definitions

Diagnosis of DDS included heterozygous germline mutations of *WT1* (Niaudet and Gubler 2006). Hypertension was defined as ≧ Stage 2 (= 95th percentile + 12 mmHg) according to the clinical practice guidelines of the American Academy of Pediatrics for screening and management of high blood pressure (Flynn et al. 2017). ESRD was defined as the requirement for chronic renal replacement therapy. DDS onset was defined as the day of discovery of the disease. Circulating renin was measured indirectly using plasma renin activity. The normal baseline plasma aldosterone concentration and PRA according to age were estimated using the Japanese baseline levels reported by Kojima (1979).

Treatment strategy for patients with DDS at our center

Dialysis was begun when patients showed progression to ESRD. A bilateral nephrectomy was performed at about age 1 year when possible to prevent progression to Wilms tumor. Renal transplantation was performed after patients were sufficiently mature.

Statistical analysis

The Mann-Whitney *U* test was used to compare continuous variables. Fisher's exact test was used to compare categorical variables. A two-sided P value of < 0.05 was considered statistically significant. All statistical analyses were performed using the JMP software package for Windows, 13.0.0 (SAS Institute Japan, Ltd., Tokyo, Japan).

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labour and Welfare, Japan and was approved by the institutional ethics committee of the National Center for Child Health and Development (Approval No. 2019-157). Written informed consent for participating in this study was obtained from their guardians.

Results

Patient characteristics

Between 2013 and 2019, six infants at our center received the diagnosis of DDS. Hypertension developed in all the patients.

Table 1 shows the clinical characteristics of the six

Table 1. Clinical characteristics of six patients with Denys-Drash syndrome.

Case	Age at onset (days)	Gestational age (weeks)	Birth weight (g)	*WT1* mutation	Nephropathy	Gonadal dysgenesis	Wilms tumor	Nephrectomy	Age at nephrectomy (Months)	Observation period (years)
1	13	39	2,882	c.1282T>C (p.Cys428Arg)	+	−	+	Bilateral	19	5.6
2	3	37	2,685	c.1300C>T (p.Arg434Cys)	+	+	−	Bilateral (preventive)	12	1.9
3	6	37	2,904	c.1300C>T (p.Arg434Cys)	+	+	−	Unilateral (preventive)	22	4.6
4	2	36	2,456	c.1301G>A (p.Arg434His)	+	+	−	Bilateral (preventive)	11	3.7
5	182	37	2,652	c.1301G>T (p.Arg434Leu)	+	−	−	Bilateral (preventive)	10	1.7
6	142	39	2,762	c.1384C>T (p.Arg462Trp)	+	−	−	Bilateral (preventive)	12	0.7

Table 2. Detailed clinical manifestations at onset.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Day of discovery (days)	13	3	6	2	182	142
Initial presentation	Edema Vomiting Poor feeding Weight gain Hypospadias Cryptorchidism	Hypertension Oliguria	Edema Poor feeding	Oliguria	Edema Vomiting Poor feeding	Edema Vomiting Weight gain
BUN (mg/dL)	26.2	26.0	15.0	27.0	45.3	37.0
Creatinine (mg/dL)	1.8	1.0	0.8	1.9	2.6	1.0
Albumin (g/dL)	1.6	2.3	1.2	1.3	1.3	1.2
Urine output at onset (mL/kg/h)	0.9	2.6	4.4	0.3	0	0.3
UP/Cr (g/g·Cre)	76.9	30.3	97.0	213.1	N.A.	N.A.

UP/Cr, urine total protein/creatinine ratio; N.A., not available.

patients with DDS. The patients (Cases 1-4) in the present study overlapped with those in our previously published report (doi: 10.1007/s10157-019-01732-7) (Nishi et al. 2019). None received the diagnosis of neonatal asphyxia. Nephropathy developed in all the patients at the onset of DDS and progressed to ESRD. One patient had the complication of Wilms tumor and underwent chemoradiotherapy and a bilateral nephrectomy. Although a preventive bilateral nephrectomy was attempted in the remaining five patients, the attempt was discontinued in Case 3 due to perioperative hypotension after removal of the left kidney. The median age at nephrectomy was 12 months (range: 10-22 months). The median observation period was 2.8 years (range: 0.7-5.6 years). All the patients were alive at the last follow-up. Only one patient received a renal transplantation.

Clinical manifestation at onset

The median age at diagnosis was ten days (range: 2-182 days). Each detailed clinical manifestation at onset is shown in Table 2. The most common initial presentation was edema. Oligohydramnios during the fetal stage and large placenta (placental/fetal weight ratio > 25%) each occurred in three of six patients. None of the patients showed neonatal pneumothorax development. The median serum BUN and creatinine at onset was 26.8 mg/dL (range: 15.0-45.3 mg/dL) and 1.4 mg/dL (range: 0.8-2.6 mg/dL), respectively. All the patients were in the nephrotic state at diagnosis. The median urine total protein/creatinine ratio and serum albumin was 87.0 g/gCr (range: 30.3-213.1 g/gCr) and 1.3 g/dL (range: 1.2-2.3 g/dL), respectively. Three of six patients had anuria or oliguria (< 0.1 mL/kg/h) at diagnosis. The median duration from onset to ESRD was only 7.5 days (range: 0-17 days).

Hypertension

Each clinical manifestation of hypertension during follow-up is shown in detail in Table 3. Five of six patients had severe hypertension by volume overload along with rapid progression to ESRD at the predialysis stage. Hypertension at the predialysis stage occurred at median three days (range: 0-5 days) from onset. The median BNP, PRA, and aldosterone was 3,483 pg/mL, 12.5 ng/mL/hr, and 5,355 pg/mL, respectively. BNP increased in all the

Table 3. Detailed clinical manifestations of hypertension event at each stage.

	HT in pre dialysis stage							HT in dialysis stage							HT in dialysis stage after nephrectomy						
Case	Age (days)	Days to develop HT from onset	Max BP (mmHg)	BNP (pg/mL)	PRA (ng/mL/hr)	Aldosterone (pg/mL)	Antihyperten-sives	Age (days)	Days to HT development from start of dialysis	Max BP (mmHg)	BNP (pg/mL)	PRA (ng/mL/hr)	Aldoste-rone (pg/mL)	Antihyperten-sives	Age (months)	Days to HT development from nephrectomy	Max BP (mmHg)	BNP (pg/mL)	PRA (ng/mL/hr)	Catecholamine (Adrenaline/ Noradrenalin/ Dopamine) (pg/mL)	Antihyperten-sives
1	16	3	120/-	612	1.4	155	None	42	20	120/-	19	150	1,320	Amlodipine (po) Nifedipine (po) Lisinopril (po)	56.4	1,096	167/94	159	< 1.0	97/209/27	Amlodipine (po)
2	4	1	114/69	3,544	15	1,610	Amlodipine (po) Nifedipine (iv)	11	2	95/56	12	100	117	Amlodipine (po) Nifedipine (po) Prazosin (po) Clonidine (po) Lisinopril (po) Candesartan (po) Propranolol (po)	12.7	1	162/104	257	0.2	N.A.	Amlodipine (po) Nifedipine (po) Prazosin (po)
3	8	12	90/-	168	N.A.	N.A.	None	26	7	112/60	22	140	438	Lisinopril (po) Amlodipine (po) Nifedipine (po) Nifedipine (iv)	22.7	26	130/80	11.3	63	N.A.	Candesartan (po)
4	5	3	110/60	N.A.	N.A.	N.A.	Amlodipine (po) Nifedipine (po)	46	44	128/-	11	13	37	Amlodipine (po) Lisinopril (po) Candesartan (po)	11.5	14	146/100	79	< 0.1	25/ 515 /31	Amlodipine (po) Nifedipine (po)
5	187	5	150/100	6,048	420	9,100	Amlodipine (po) Nifedipine (po) Prazosin (po) Nifedipine (iv)	197	9	117/46	10	60	58	Candesartan (po)	14.2	95	120/58	7.7	< 0.1	259/831/57	Amlodipine (po) Prazosin (po)
6	142	0	130/80	3,423	10	20,100	Amlodipine (po) Nifedipine (po) Prazosin (po) Nifedipine (iv)	171	12	188/50	12	120	528	Candesartan (po) Amlodipine (po)	12.8	0	138/92	20	< 0.1	172/ 471/ 23	Amlodipine (po) Nifedipine (po)
Med	16	3		3,483	12.5	5,355		44	10.5		17	110	277.5		13.5	20		49.5			

Case 3 underwent only left nephrectomy. HT induced by fluid administration was excluded in the postnephrectomy dialysis stage.
Normal range of BNP: 0.0-18.4 pg/mL.
Normal range of PRA and aldosterone: 8.8 ± 8.7 ng/mL/hr and 627 ± 485 pg/mL (0-6 days of age)
7.4 ± 3.7 ng/mL/hr and 522 ± 235 pg/mL (7-27 days of age)
5.7 ± 3.0 ng/mL/hr and 382 ± 210 pg/mL (1-2 months of age)
3.5 ± 2.0 ng/mL/hr and 299 ± 190 pg/mL (3-5 months of age)
2.6 ± 1.4 ng/mL/hr and 174 ± 96 pg/mL (6-11 months of age)
2.1 ± 1.1 ng/mL/hr and 142 ± 76 pg/mL (1-2 years of age)
1.8 ± 1.0 ng/mL/hr and 114 ± 65 pg/mL (3-5 years of age)
1.4 ± 0.6 ng/mL/hr and 97 ± 45 pg/mL (6-8 years of age)
Normal range of catecholamines: dopamine < 30 pg/mL, norepinephrine < 70 pg/mL, adrenalin 100-400 pg/mL.
HT, hypertension; PRA, plasma renin activity; Med, median; N.A., not available.

Table 4. Summary of antihypertensive agents used at each DDS disease stage.

	Predialysis stage	Dialysis stage	After bilateral nephrectomy	At last follow-up (after bilateral nephrectomy)
Number of patients who received antihypertensive agents (n)	4/6	6/6	3/5	4/5
The average number of antihypertensive agents administered (n)	2.4	3.3	1.4	1.4
ACE-I and/or ARB (n)	0/0	6/6	0/5	0/5
Main cause of hypertension	Hypervolemia due to ESRD	High plasma renin activity	High catecholamine and/or hypervolemia	High catecholamine and/or hypervolemia

ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; ESRD, end-stage renal disease.

patients in whom it was measured. All the patients required emergency dialysis. The average number of antihypertensive agents administered was 2.4 (range: 0-4). Hypertension in all the patients improved by dialysis and use of antihypertensive agents without angiotensin-converting-enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB). The patient (Case 3) suffered from severe hypotension due to septic shock and cardiopulmonary arrest at age 8 days. Just after this event, she immediately showed progression to ESRD and required dialysis.

All the patients required antihypertensives at the dialysis stage. The median number of days from the start of dialysis to requiring antihypertensive administration was 10.5 (range: 2-44) (Table 3). The average number of antihypertensive agents administered was 3.3 (range: 1-7). All the patients received ACE-I and/or ARB. Five patients still needed multiple antihypertensive agents. The median level of BNP, PRA, and aldosterone was 17 pg/mL, 110 ng/mL/hr, 277.5 pg/mL, respectively. PRA increased in the all patients. Four of six patients in the dialysis stage measured values of PRA and aldosterone after ACE-I or ARB administration. ACE-I and/or ARB ameliorated the hypertension in all the patients.

After an emergency bilateral nephrectomy, three of five patients completely discontinued use of antihypertensive agents. However, one patient required antihypertensive treatment 14 days after the procedure. Two patients had hypertension and required antihypertensive treatment immediately after their bilateral nephrectomy, and PRA decreased to an almost undetectable level. The plasma catecholamine was elevated in two patients with hypertension in whom it was measured. Additionally, the median levels of BNP were high. At the last follow-up, four of the five patients required an average of 1.4 antihypertensive agents, and none needed ACE-I or ARB.

A summary of antihypertensive agents administered at each stage is shown in Table 4. The main causes of hypertension were hypervolemia in the predialysis stage, renin-associated hypertension in the dialysis stage, and multiple factors, including increased plasma catecholamine-associated hypertension and/or hypervolemia in the postnephrectomy dialysis stage.

Target-organ complications of hypertension

No acute end-organ damage, such as hypertensive encephalopathy, heart failure or ocular complications secondary to hypertension, developed in any of the patients. At the last follow up, all the patients showed left ventricular hypertrophy. The median IVSd, LVPWd, and E/E' value was 2.1 SD (range, –0.7-4.9 SD), 1.0 SD (range, –0.9-5.2 SD), and 8.8 (range, 2.8-14.0), respectively.

Hypotension after nephrectomy

In one patient (Case 1), hypotension requiring fluid administration persisted for two days after a bilateral nephrectomy. One patient (Case 3) experienced perioperative refractory hypotension requiring catecholamine and fluid administration immediately after the left nephrectomy; the right nephrectomy was not performed. Preoperative PRA and aldosterone were 120 ng/mL/hr and 9,000 pg/mL in Case 1 and 330 ng/mL/hr, 6,150 pg/mL in Case 3, respectively.

Discussion

In this retrospective investigation, we demonstrated the detailed clinical manifestations of severe hypertension in patients with DDS. It is important to note that hypertension requiring treatment with multiple antihypertensive agents is complicated in cases of DDS. The cause and management of hypertension in DDS vary depending on the disease stage. The main cause of hypertension is hypervolemia due to renal failure at the predialysis stage, renin-associated hypertension at the dialysis stage, and multiple factors, including increased plasma catecholamine-associated hypertension and/or hypervolemia at the postbilateral nephrectomy dialysis stage.

In as early as the predialysis stage, hypertension was observed at a median three days from the day of discovery. Although PRA and aldosterone were high, hypertension in all patients improved by dialysis without ACE-I and ARB

administration. Therefore, the main cause of hypertension was assumed to be hypervolemia due to renal failure. Neonatal onset DDS should be considered in the differential diagnosis of congenital nephrotic syndrome (Nishi et al. 2019). Frequent albumin infusions such as those given to patients with congenital nephrotic syndrome of the Finnish type will exacerbate hypertension in a patient with neonatal onset DDS.

In the dialysis stage, hypertension was observed at a median of 10.5 days from the start of dialysis. Most patients had high PRA, and hypertension was reduced in all patients by ACE-I and/or ARB administration in our study. Although the median levels of aldosterone were not high, it could be possible that the PRA and aldosterone values of the four of the six patients were measured after ACE-I or ARB administration in the dialysis stage. Regional ischemia induced by rapid progression to ESRD may play a major role in increasing PRA and hypertension. Andreas et al. showed that renin gene transcription is regulated by the WT1 protein (Steege et al. 2008). Luciana et al. showed that the potential for interaction between heat shock protein 70 and vitamin D receptor was related to mitochondrial disturbances, as hypertension precursors could be a consequence of WT1 modulation (Mazzei et al. 2017). These facts may partially explain the findings in patients with hypertension due to increased PRA at the dialysis stage.

In the postnephrectomy dialysis stage, PRA was no longer detected, and ACE-I and ARB were no longer required for treatment in all the patients. Nevertheless, in some patients with DDS, hypertension becomes a problem after bilateral nephrectomy, possibly due to the failure of homeostasis re-establish after a prolonged period of dysregulation of chemical and fluid balance. Hypertension in patients with chronic kidney disease is common and likely associated with more rapid deterioration of kidney function (Mitsnefes et al. 2003; Wilson and Flynn 2020). A variety of factors may contribute to the increased prevalence of hypertension in patients with chronic kidney disease, such as sodium retention, sympathetic nervous system dysfunction, secondary hyperparathyroidism, erythropoietin treatment, impaired nitric oxide synthesis, and endothelium-mediated vasodilation (Raine et al. 1993; Neumann et al. 2004; Passauer et al. 2005). In present study, the cause of hypertension after a bilateral nephrectomy also might have arisen as a result of multiple factors, including increased plasma catecholamine and hypervolemia. Both sympathetic nerve activity and the renin-angiotensin system are important in counteracting decreased systemic arterial blood pressure (Henriksen et al. 1985). Furthermore, catecholamine reportedly enables the release of renin (Bunag et al. 1966). Although the precise cause of increased plasma catecholamine in the present case was unclear, it may have been part of a compensatory mechanism to maintain blood pressure against changes due to the loss of PRA.

We should be careful and be aware that not only hypertension but also postnephrectomy hypotension could occur in the patients with DDS, as this condition developed in two patients in the present study. Angenita et al. reported the case of a female neonate with chronic renal failure following prenatal exposure to ACE-I and that of a 4-month-old infant with congenital nephrotic syndrome in whom persistent arterial hypotension developed following a bilateral nephrectomy (van Lieburg and Monnens 2001). Amanda et al. reported the case of a 10-month-old infant with DDS complicated with phenylketonuria in whom refractory hypotension developed following a bilateral nephrectomy (Hassinger and Garimella 2013). Bilateral and unilateral nephrectomies can cause hypotension in DDS due to decreased PRA. Because renin is part of an important backup mechanism for maintaining blood pressure, the possibility of hypotension after renin loss in patients with a nephrectomy should be borne in mind.

Because the cause of hypertension in DDS varies depending on disease stage, the strategies for administering antihypertensive agents at each stage may be summarized as follows: 1. In the predialysis stage, Ca blockers, prazosin, and/or clonidine are recommended. If the condition progresses to ESRD, volume control by dialysis is necessary; 2. In the dialysis stage, the use of antihypertensives, including ACE-I and/or ARB, is recommended; 3. In the dialysis stage following a bilateral nephrectomy, ACE-I and ARB administration can be stopped, and the use of Ca blockers, prazosin, and/or clonidine is recommended. At any stage, other possible causes of hypertension, such as hypervolemia, secondary hyperparathyroidism, and treatment with erythropoiesis-stimulating agents, should be considered, and the appropriate treatment should be administered.

There are several limitations to the present study. First, although BNP is used as a marker of intravascular volume status, a previous study reported that BNP was not significantly associated with intravascular volume status (Takahashi et al. 2013). In the present study, however, intravascular volume status was assessed comprehensively without relying solely on BNP. Second, the plasma PRA and aldosterone measurements may not be precise due to the effect of various factors, such as body posture, time of day and medications (Kojima 1979). Third, this study was a retrospective study conducted at a single center with a small number of patients due to the rarity of this monogenic disease. The clinical manifestations of DDS vary widely. While all the patients with DDS in the present study showed rapid progression to ESRD from its onset in the neonatal period, the results of this study may not necessarily be extrapolatable to all cases of DDS.

In conclusion, hypertension in infantile-onset DDS is a common complication which can persist throughout a patient's life. Further, physicians should be alert to the possibility of perioperative hypotension in patients with a nephrectomy. The management of blood pressure is crucial in a therapeutic strategy that takes into account the disease stage and pathology of patients with infantile-onset DDS.

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Conflict of Interest

All authors declare no conflict of interest concerning the present study.

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