CASE REPORT

Renal denervation for severe hypertension in a small child with Turner syndrome: miniaturisation of the procedure and results

Alice Bonanni,¹ Francesco Pasetti,² Gian Marco Ghiggeri,¹ Carlo Gandolfo²

¹Division of Nephrology, Dialysis and Transplantation, Istituto G Gaslini, Genoa, Italy
²Interventional Radiology and Neuroradiology Unit, Istituto G Gaslini, Genoa, Italy

Correspondence to
 Dr Gian Marco Ghiggeri,
 GMarcoGhiggeri@ospedale-gaslini.ge.it

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SUMMARY

Sympathetic nervous system hyperactivity plays a role in development and progression of hypertension. While renal denervation employing radiofrequency devices has been used therapeutically in treating severe hypertension with alternate results in adults, few data are available regarding children. We treated a 6-year-old girl affected by Turner syndrome presenting severe hypertension and an episode of stroke, in spite of treatment with four antihypertensive drugs, with sympathetic ablation. The Simplicity device (Medtronic, Minneapolis, USA) was adapted to the smaller vessels, allowing a tailored approach. After 3 and 6 months of treatment, and β -blocker discontinuation, blood pressure values were set between the 90th and 95th centiles for sex and age, and normalised at 12 months. We confirm that renal denervation can be used to treat severe hypertension in children; miniaturisation of catheter and tailoring the procedure for small vessels allowed a safe approach. Progressive improvement of blood pressure had a satisfactory clinical impact.

BACKGROUND

Resistant hypertension is defined as blood pressure (BP) above the target of 90th centile of the normal range in presence of optimal doses of three or more antihypertensive medications (one ideally being a diuretic), or BP requiring four or more agents to achieve control.^{1 2} Although the pathogenesis is considered generically multifactorial (here including living conditions, stress, food, smoke, etc), single mechanisms play specific roles. Hyperactivity of the sympathetic nervous system (SNS), for example, promotes mineralocorticoid-dependent salt and water retention leading to sodium and liquid overload.³ The clinical rebound is a direct correlation between BP and sympathetic activity, a finding common in patients with severe hypertension. Experimental models support the important role of the SNS in regulation of BP.⁴ Based on this, interruption of the renal SNS by sympathetic denervation has been tentatively used therapeutically in adults affected by resistant hypertension but with contrasting conclusions.^{5–8} In the Simplicity HTN-3 trial,⁸ 535 adults were randomised to denervation and, after 6 months, a trend was shown for patients to have a reduction in BP compared to patients receiving a simulated procedure. This study represents the most advanced application of renal denervation in human beings, but also summarises some of the inconsistencies connected with its application. In fact, the change in systolic

pressure in the denervation group versus patients receiving a simulated procedure was not statistically different, probably due to the quality of the technical performance (four-quadrant ablation vs one quadrant), which limited the final interpretation of results.⁹ A key message of the Simplicity HTN-3 trial is that a proper application of the procedure is crucial to results.

To the best of our knowledge, there is only one report in the literature, describing the case of a 16-year-old boy with aortic coarctation in whom renal denervation improved hypertension after surgical repair of the aortic problem.¹⁰ We describe a young child 6 years of age affected by Turner syndrome who underwent denervation for severe hypertension. Considering the lack of literary data, our case is of particular interest in view of the age of the patient; she required miniaturisation of the approach since it was unclear whether the device used for adults could be tailored for children under 10 years of age. The key question on the possibility of achieving full circumferential ablation in children is crucial to envisage the extension of the procedure to intractable hypertension for those under 10 years of age. In this study, we decided to use the Simplicity device (Medtronic, Minneapolis, USA) adapted to the smaller vessels of a 6-year-old girl in whom severe hypertension (in spite of 4 drugs being administered) had led to a stroke a few months before. The particular importance of the clinical features and a real possibility of further neurological episodes led us to undertake this innovative approach in spite of the risks. The positive results would stimulate physicians to extend the use of renal ablation to other children with unresponsive hypertension and stabilise interventional guidelines for a proper approach.

CASE PRESENTATION

We present a case of a 6-year-old girl presented to our hospital with severe hypertension.

The child's medical history was unremarkable until November 2012, when, during an attack of viral gastroenteritis, she had difficulty walking, associated with neck pain, tremor and loss of function of her left arm and leg. The full picture of left stroke developed within a few days. The neurological examination at onset was conducted in a Ukrainian hospital and showed bilateral positivity of Babinski sign, leg hypertonia and hyper-reflexia (greater on the right), and no meningeal signs (table 1).

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Table 1 Results of neurological examination at onset and at 6-month follow-up

Neurological examination	Onset	6-Month follow-up
Cranial nerves	Uninjured	Uninjured
Meningeal signs	Absent	Absent
Muscular trophism	Within normal limits	Within normal limits
Muscle strength	Preserved in upper extremity, poor in lower extremity	Preserved in upper extremity, improved in lower extremity
Upper extremity coordination	Performer without dysmetria	Performed without dysmetria
Babinski sign	Bilaterally positive	Bilaterally positive
Osteotendinous reflexes	Increased	Increased
Ambulation	Lack of autonomous maintenance of erect standing; spastic ambulation with bimanual active support and trunk anteversion	Autonomous maintenance of erect standing; spastic ambulation without support

Bold in Table 1 indicates the improvement of neurological signs after renal denervation.

The patient was subsequently transferred to our centre, where she was diagnosed with Turner syndrome with severe hypertension and associated organ damage (papilloedema and initial left ventricle hypertrophy).

The brain MRI documented prior haemorrhagic microareas at frontal lobe, medulla oblongata, spinal cord and left opercular region (insular and occipital lobes; [figure 1A–C](#)). Moreover, a mesoaortic syndrome, characterised by mild reduction of aorta calibre, without renal arteries stenosis, was seen on angio-MRI.

Other causes of secondary hypertension were excluded on the basis of the clinical work up.

BP control was inadequate in spite of an association therapy with maximal doses of calcium antagonist, β -blocker, ACE inhibitors and clonidine. The ambulatory blood pressure monitoring (ABPM) showed median BP of 132/91 mm Hg with peak values up to 156/124 mm Hg. Lack of a significant pressure gradient due to reduced aorta calibre excluded endovascular angioplasty and posed, on an emergency basis, the possibility of an interventional procedure such as renal ablation, although it was never used in children.

TREATMENT

Following angiographic confirmation of homogeneously small but otherwise normal renal arteries ([figure 2A](#)), the patient underwent renal denervation under general anaesthesia with overlapping pain management therapy. The Simplicity device was adapted to the smaller vessels bearing in mind the thinner wall structure that confers greater sensitivity to current pulses. Based on geometrical considerations (wall thickness and inner side area of cylindrical vessels), the advised overall low-level radiofrequency energy was split and delivered as reported in [table 2](#). Respectively, five and four series of 8W ablations of approximately 70–80 s each were delivered to left and right renal arteries at unique locations following a spiral pattern in order to maintain a safe and effective renal procedure. Denervation notches were recognised as markers of effective contact between catheter tip and artery wall.

The postoperative angiographic control showed no signs of renal artery dissection or leak of contrast medium ([figure 2B](#)). Continuous intra-arterial nimodipine infusion was performed through the guiding catheter (2 mg in 500 mL of saline).

Figure 1 MRI: sagittal (A) and axial (B and C) susceptibility-weighted images depicting dotting signal loss (thin white arrows) into the medulla oblongata (A and C), spinal cord (A) and left opercular region (insular and occipital lobes (B)), specific for hypertensive haemorrhagic sequelae.

Figure 2 Miniaturisation of renal denervation procedure: (A) unsubtracted digital angiography showing the small diameter of the right renal artery; the most distal positioning of the tip of the renal denervation catheter targeted the superior branch (white arrow head). (B) The final angiographic control showing multiple spasms with no sign of dissection (black arrow head).

The overall time for the procedure, including patient preparation and care after sedation, was 300 min. No intraprocedural or periprocedural complications occurred.

OUTCOME AND FOLLOW-UP

β-Blockers were discontinued soon after the procedure due to rapid decrease of BP values. At 3-month follow-up, median diurnal and nocturnal BP values registered by ABPM were 125/79 and 111/72 mm Hg, respectively, representing improved values, but always above the 90th centile for age and sex. The same trend was observed at 6 months (median diurnal and nocturnal BP values 120/77 and 112/75 mm Hg, respectively). The therapy was therefore no further reduced. Nevertheless, general conditions were improved, with notable regression of neurological signs as compared to neurological examination at onset (ie, muscle strength, improved ambulation; [table 1](#)).

Moreover, as already observed in the literature,^{11 12} we obtained a cardiological effect, as demonstrated by a resolution of ventricular hypertrophy at echocardiography.

The ABPM monitoring at 12 months showed a further improvement in BP control, with median diurnal values of 115/75 mm Hg, thus located below the 75th centile for sex and age. Nevertheless, physiological nocturnal dipping was not preserved, thus requiring continuation of current therapy. The trend of diurnal BP values at follow-up is shown in [figure 3](#). Moreover, the fundus oculi performed at 12 months from renal denervation showed a significant bilateral reduction of papilloedema, while the optical coherence tomography revealed a thinning of the retinal nerve fibre layer thickness, as a consequence of previous hypertensive damage ([figure 4](#)).

Table 2 Renal denervation procedure form

Renal artery side	Orientation	Impedance (Ω) at start	Duration of treatment (s)
Right	Inferior	236	–
Right	Superior	240	–
Right	Lateral	240	36
Right	Superior	227	45
Left	Inferior	222	–
Left	Inferior	215	–
Left	Superior	230	–
Left	Superior	247	37
Left	Superior	235	30

DISCUSSION

Interruption of the renal SNS by sympathetic denervation has already been studied in adults with resistant hypertension. Results are still under debate but there is a consensus in extending the procedure after adequate modifications and controls. The Simplicity-1 study⁴ (an unblinded, proof-of-principle study without a control group) demonstrated a sustained BP reduction at 24-month follow-up. The results of the Simplicity-HTN-2 study were also encouraging.⁵ Nevertheless, although the study was designed as a randomised control trial, the open-label administration of the treatment did not permit exclusion of a placebo effect. The Simplicity-HTN-3 study,⁶ a prospective, single-blind, controlled, randomised trial, was designed to overcome the above problems and conducted at 88 US centres. This study showed a trend but failed to meet the primary efficacy end point of reduction of BP at 6 months; nevertheless, it did achieve the safety end point. There were basic procedural discrepancies that limited interpretations of data and made it necessary to go a further step. Differences in results obtained by four-quadrant ablation (performed in both kidneys in only 19 patients and in one kidney in 68 patients) were marked, implying that a correct procedure achieving a 360-grade ablation is crucial to effects. This clearly posed the problem of how to apply a correct procedure to children.

We present a paediatric case of renal denervation in a young girl with resistant hypertension. Versatile catheter and geometrical considerations allowed a treatment tailored to the size of the patient. Delivering of energy schemes was defined on the basis of careful discussion with bioengineers. The procedure was effective and safe. After 6 months we obtained a partial result

Figure 3 Blood pressure (BP) levels at follow-up: trend in ABPM medium BP levels at follow-up after renal denervation. Only at 12-month follow-up did we reach an adequate BP control, with values <75th centile for sex and age.

Figure 4 Fundus oculi and optical coherence tomography (OCT) at baseline and 1-year follow-up: fundus oculi showing a significant bilateral reduction of papilloedema at 12 months as compared to onset (white arrow). OCT graphs on the right showing a thinning of the retinal nerve fibre layer thickness, as an expression of previous hypertensive damage.

based on diurnal reduction of BP in spite of withdrawing β -blockers; normalisation was achieved at 12 months. Overall, we obtained an improvement in general clinical status that included near-normalisation of neurological symptoms.

Renal denervation could represent a therapeutic evolution in selected paediatric patients with hypertension resistant to drugs. Standardisation in children is a difficult task due to the different parameters of potential patients. This report could serve as a

template to set an operative procedure, that is, dose–energy and sites of application, which must be tailored for other patients on the basis of age and size.

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Contributors CG, AB and GMG were responsible for procedure concept and design. CG and FP were involved in renal denervation. AB and GMG for manuscript drafting. Critical revision of the manuscript for important intellectual content and final approval: all authors.

Competing interests None.

Patient consent Obtained.

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Patient's perspective

On 5 December 2014, the patient's grandmother wrote: Thanks to you and your co-workers; my niece now feels better and her blood pressure is well controlled with few drugs. She goes to school, studies happily, is very active in school activities and the teachers are very satisfied.

Learning points

- Severe hypertension resistant to drugs (≥ 3 antihypertensive medications taken) is a major challenge in paediatric patients. Cases with neurological problems pose a clinical solving emergency that requires rapid answers.
- Sympathetic denervation is an option. It has already been used in adults and in just one adolescent with resistant hypertension, with promising results. The Simplicity-HTN-3 randomised trial clearly showed the necessity of a proper four-quadrant procedure to achieve clinically relevant reduction of blood pressure (BP) at 6 months.
- We present the first paediatric case (patients under 10 years) treated with renal denervation. Versatile catheter and geometrical considerations allowed a tailored approach, delivering energy in an effective and safe way. They may constitute the basis to discuss and share guidelines for renal denervation in children.
- Results showing 'quasi' normalisation of BP levels at 6 months (90th centile) and further reduction at 12 months (<75th centile) in spite of discontinuation of the drug load may be deemed satisfactory and worth considering as an approach to successfully treating intractable hypertension.

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