A Complicated Case of Resistant Hypertension

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Abstract- A 47-year-old woman presented with a history of resistant arterial hypertension, associated with disabling headache. She was subjected to an enormous number of tests in order to identify an underlying cause of secondary hypertension, such as pheochromocytoma or Cushing syndrome, but all the most common causes of secondary hypertension were investigated and gradually excluded. Factitious use of amphetamine or cocaine was excluded, and therapy compliance was verified by witnessed ingestion of drug therapy, in order to rule out Munchausen syndrome. The patient underwent a first transcatheter renal denervation (RDN) with poor effect on blood pressure (BP) at long term follow up. Because of extremely poor control of BP values, a second RDN was performed two years later, again with inadequate long term efficacy. Despite an uncontrollable pre-procedural BP, RDN had an excessive BP lowering effect in this patient, but only for few months. In conclusion, a definitive diagnosis was not performed in our patient, despite an extremely deepened examination of the most common cause of refractory hypertension.

Keywords: Hypertension; Refractory hypertension; Renal denervation

Introduction

Resistant hypertension (RH), a clinical condition in which patients cannot control their BP despite the use of a diuretic and at least two other drugs with the complementary mechanism of action, (1) is a relatively common problem in developed countries. Indeed, about 10% of all hypertensive patients in the USA are affected by RH (2). Among higher risk populations (e.g. diabetes mellitus, obesity and chronic renal disease) the proportion of uncontrolled patients is even higher (3). New devices-related treatment for patients with RH was born, but they are not risk-free. Thus, a meticulous investigation of the patient is extremely important, in order to identify those who could obtain a benefit by these invasive procedures without an elevated risk of their drawbacks. We report a case of a patient with idiopathic and uncontrolled RH despite the use of optimal medical therapy and double renal denervation (RDN).

Case Report

Our patient, D. B. (who provided written consent for this case report) is a short (body mass index 27.5 kg/m²) 47-year-old Caucasian woman, who was normotensive until 40-year-old. She is known for Reynaud phenomenon and familiarity for essential hypertension, but not for cerebrocardiovascular disease. Hypertension was diagnosed in 2007; by that time, her BP values progressively rise, until the patient presented in January 2012 in ER with an occipital and supraorbital headache and an arterial BP of 215/105 mmHg. After this hypertensive crisis, her BP measured at the office (4) was noted to be consistently elevated in the range of 180/100 mmHg on three occasions. Therefore, her therapy was potentiated, and she started treatment with telmisartan, nebivolol, amloidpine, and hydrochlorothiazide. In March 2012 she came to ER for a new hypertensive crisis (BP 220/100 mmHg) despite a new upgrade of her therapy (Figure). She was admitted to our hospital, and she was tested for the most common causes of secondary hypertension: renin activity and aldosterone values were within normal range; renal arteries Duplex-Doppler study ruled out renal arteries stenosis; metanephrine, normetanephrine, and 24-hour urinary catecholamines were also in the normal range. There were no differences in BP values between lower and upper extremities. Aortic coarctation, renal parenchymal disease, and Cushing syndrome were also ruled out using abdomen ultrasound and thoracic and abdominal thin-slice computer tomography, while...
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encephalic MRI allowed excluding hypophys
pathologies. Last, 24-hour urinary collection of drug
metabolites such as cocaine or amphetamine was always
unremarkable (Table 1). In consideration of her high BP
types, measured also with 24-hour BP monitoring
(180/100 mmHg), she was also tested for organ
damages, without any pathologic findings (Table). Her
fundus oculi revealed a normal arterial microcircula
tion, and no pathologic findings resulted from
echocardiogram, supra-aortic branches, and renal
arteries echo-doppler studies or encephalic and abdomen
MRI. More than one urinalysis was performed, always
without detection of proteinuria, and no electrolytes
alteration was found in the 24-hour specimen.
Antihypertensive therapy was further increased to the
maximum tolerated posology of telmisartan and nebivolol,
with canrenone in addition to the old therapy
regimen (Figure).

In June 2012, because of evidence of refractory and
uncontrolled hypertension, she had admitted again to our
hospital for RDN, done with the Ardis Symplicity
device (Medtronic Inc., Minneapolis, USA). The
procedure was performed with apparently acute optimal
and encouraging results (invasive arterial BP
measurement on therapy during the procedure: 160/100
mmHg; 24-hour BPM at discharge: 100/60 mmHg)
(Table 1). After the RDN she complained about
palpitation and collapse due to orthostatic hypotension,
and she was discharged with only propranolol, in order
to control her reflex tachycardia (Figure). During the
following summer months, her BP values were well
controlled, with even some episodes of collapse for low
BP (Figure). However, long term results of the RDN
were disappointing: at the beginning of the cold season
her BP values raised again, usually with peaks in the
afternoon, and her therapy was gradually improved
again, until February 2013, when she came to ER for a
new hypertensive crisis (210/120 mmHg). She was
hospitalized to retest contingent organ damages and to
upgrade her therapy (Table). At that time, a self-blood
pressure measurement (S-BPM) at home was
recommended. The patient was provided with a
validated, fully automated home S-BPM device (A and
D UA-767PBT, A and D Company, Japan) and was
instructed to perform 2 home BP measurements,
separated by 5 minutes of rest and in the seated position,
at least two times per day, morning and evening. Home
BP readings were recorded by the patient in a log book
and in CARDIOcheckAPP (medical app for iOS and
Android platforms, by Medical Mate srl, Italy) in order
to share, by smartphone, self-tested BPMs with her
cardiologist (data summarized in Figure). As in the
previous year, her BP was well controlled in case of hot
temperature, with the need to reduce the therapy in the
summer or in the case of stay in hot countries for some
hypotensive episodes, but it rose again in the winter
until she had a new hypertensive crisis in February
2014. Indeed, on this occasion, she came back to our ER
with an occipital and supraorbital headache (BP:
200/120 mmHg), and she was re-hospitalized. During
the hospitalization, she performed other screening exams
for organ damages and for more uncommon causes of
secondary hypertension, (immunologic diseases such as
vasculitis, systemic sclerosis, systemic lupus erythematosus, Sjogren’s syndrome, polyarthritis nodosa, antiphospholipid syndrome), by serology and
nailfold capillaroscopic, both negatives for autoimmune
rheumatic diseases. In addition, an evaluation with the
Endo-PAT 2000 system was performed, with a resultant
pattern of augmented arterial stiffness (5). Furthermore,
24-hour BP monitoring showed lack of control of her BP
despite the maximum tolerated medical therapy.

After multidisciplinary discussion, also including
specialists beyond the area of cardiovascular medicine
(neurologists and nephrologists), it was agreed new
indication for RDN, performed this time with an
ultrasound denervation system, the ReCor Paradise
(ReCor Medical, Ronkonkoma, NY, USA). Like the first
time, the procedure was acutely very effective (invasive
arterial BP measurement on therapy during the
procedure: 220/110 mmHg; H-BPM at discharge: 90/60
mmHg). Regrettably, this time the procedure was
complicated by a prolonged hypotension (BPM 75/35)
which caused a loss of consciousness and a reduction of
the visual acuity of the left eye associated with
hyposthenia of the left lower limb. In this contest, a head
MRI was performed, and multifocal, hyperintense at a
long-TR sequence, parenchymal alterations involving
the supratentorial bilateral white matter were seen.
These lesions were interpreted as of “specific significancen” by radiologist, and a diagnosis of
functional stroke was performed (6).

After the neurological rehabilitation, she was
discharged without antihypertensive therapy.
Unfortunately, again, her BP values were adequate for
summer months, but during the winter they increased
again, with the need of increase the antihypertensive
drugs number and posology.

Even though two RDN procedures were not totally
effective, our patient has now an easier control of her BP
values, despite frequent peaks also after the second
procedure, as in the previous two years.
Figure 1. Home measurement of blood pressure (BP) and heart rate (HR) from February 2012 through August 2015 provided with a validated, fully automated home self-tested BP measurement (A and D UA-767PBT device, A and D Company, Japan), and recorded by the patient in CARDIOcheckAPP (medical app for iOS and Android platforms, by Medical Mate srl, Italy) in order to share, by smartphone, self-tested BP measurements with her cardiologist. Note the lack of efficacy for two renal denervation procedures. β-blockers were either nebivolol or propranolol; calcium antagonist: amlodipine or diltiazem; AT1 antagonist: telmisartan or irbesartan; diuretic: hydrochlorothiazide and/or furosemide; aldosterone antagonist: spironolactone; canrenone and/or amiloride; central sympatholytic: clonidine; vasodilators: doxazosin, nitroglycerin, and minoxidil; ivabradine.
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Table 1. Instrumental and laboratory examination performed after the first hypertensive crisis. BP: blood pressure; O-BPM: office-blood pressure measurement; H-BPM: hospital-blood pressure measurement; CT: computed tomography; MRI: magnetic resonance imaging; SAB: supra-aortic branches; TT: trans-thoracic; IA-BPM: invasive arterial blood pressure monitoring; S-: serum; U-: urinary; DU-: daily urinary; TSH: thyroid stimulating hormone; Aldo: aldosterone; Adr: adrenalin; Nor: noradrenaline; ACE: angiotensin converting enzyme.

<table>
<thead>
<tr>
<th>TIME</th>
<th>Instrumental examination</th>
<th>Comments</th>
<th>Laboratory test</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 2012</td>
<td>Renal arteries echo-Doppler; Abdomen echography, thin-slice CT, and MRI; encephalic MRI. Echocardiogram; Kidney echo-doppler; Fundus oculi; SAB O-BPM</td>
<td>180/100 mmHg</td>
<td>Urinalysis: no proteinuria, electrolytes alterations or presence of cocaine and amphetamine metabolites.</td>
</tr>
<tr>
<td>March 2012</td>
<td>IA-BPM 24hrs H-BPM</td>
<td>Normal</td>
<td>S-Creatin 0.82; S-Urea 33; S-Na* 140; S-K* 4.71; S-Ca** 2.44; S-Al 4.7; DU-Al 1.0, DU-Na 4.7 μg/24h, U-Na 16.5; U-Nor 29.7 μg/24h.</td>
</tr>
<tr>
<td>June 2012</td>
<td>1A-BPM 24hrs H-BPM (after 1st RDN) Head MRI Abdomen MRI gadolinium; TT-Echocardiogram. O-BPM 24hrs H-BPM</td>
<td>160/100 mmHg 100/60 mmHg Normal</td>
<td>S-Creatinine 0.85; S-Na* 141; S-K* 4.21; S-Ca** 2.35.</td>
</tr>
<tr>
<td>February 2013</td>
<td>O-BPM 24hrs H-BPM Capillaroscopy Coronarography</td>
<td>210/120 mmHg Normal NEG for vasculitis and immunologic diseases</td>
<td>S-TSH; F3; FT4; U-Nor 17; U-Adr 2.5; S-Al 139 pg/mL.</td>
</tr>
<tr>
<td>February 2014</td>
<td>IA-BPM 24hrs H-BPM</td>
<td>220/120 mmHg Normal</td>
<td>S-ACE 48 U/L (37-137); S-Al 287 pg/mL (70-350).</td>
</tr>
<tr>
<td></td>
<td>IA-BPM 24hrs H-BPM (after 2nd RDN)</td>
<td>90/60 mmHg</td>
<td>S-Renin orthostatic 2.2 μg/mL (1.5-5.7).</td>
</tr>
</tbody>
</table>

*: measured in mg/dL
*: measured in mmol/L
*: measured in μg/L

Discussion

We do not already know which could be the underlying cause of hypertension in this patient. We did not specifically look for some extremely rare causes of secondary hypertension, such as Liddle’s syndrome, type E brachydactyly, and neurovascular contact, but all imaging and laboratory exams performed and also clinical examination could reasonably lead us to rule out this sporadic conditions (5,6). Despite the relevant BP fluctuations (very low BP in the summer or in case of stay in hot countries) and the recurrence of sinus tachycardia, the absence of primary symptoms of dysautonomia (e.g. excessive fatigue, thirst, sweating and mydriasis, constipation, etc…) made us also to exclude the most common causes of autonomic dysfunction (9).

She was refractory not only to the maximum tolerated medical antihypertensive therapy but in the long term-also to a device-related antihypertensive treatment, such as the RDN. It is known from the literature that the RDN can improve BP control in hypertensive patients, but this effect is lost if reinnervation occurs, as it in many cases does (10). It is important to underline that our patient underwent RDN before the publication of the SIMPLICITY HTN-3 trial (9,10).

For us, this case revealed itself very hard to manage: extremely deep BP oscillations and post-procedural complications led us to doubt about patient’s compliance. These were the main reasons that deceived us to perform other device-related treatment, such as baroreflex stimulation or even deep-brain stimulation of the ventrolateral periaqueductal gray/ventriculocardial gray (11,12). Furthermore, we were also astonished by the absence of organ damages after many years of uncontrolled hypertension. Nevertheless, the psychiatric consultancy, the 24-hour BP monitoring and, above all, witnessed ingestion of drug therapy allowed us to rule out Münchausen’s syndrome or another form of patient nonadherence or substances abuse favoring hypertension, leaving us without a true explanation.
about the cause of this refractory hypertension.

References


