Drug resistant hypertension and Munchausen syndrome

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Abstract

A 40-year-old female presented with a history of resistant arterial hypertension associated with massive nasal bleedings. Despite being subjected to a lot of tests in order to identify a cause of secondary hypertension, all possible causes were excluded. There were no organ damages. Notwithstanding changes in the hypotensive treatment regimen and a significant escalation of pharmacological treatment, there were difficulties in achieving normal blood pressure (BP) values. Resistant hypertension was diagnosed. It was decided to perform tests to confirm the patient's use of hypotensive drugs and to search for substances increasing BP in the Department of Forensic Medicine. High urinary concentrations of pseudoephedrine and its metabolites were found using high-performance liquid chromatography. During the retrospective analysis of the case of this patient with a psychiatrist, Munchhausen syndrome was suspected.

Key words: resistant hypertension; drug abuse; Munchausen syndrome

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A 40-year-old female patient was admitted to the Department of Hypertensiology because of worsening blood pressure (BP) control lasting for about 4 months. The woman had been treated for hypertension (HT) for 17 years. During multiple previous visits to the clinic, secondary causes of HT were excluded and no features of organ damage were found. A daily urine collection was performed several times to detect elevated levels of methoxycatecholamines. The examinations were performed during the stay in the Clinic when there were elevated values of blood pressure registered both by traditional measurements and by continuous ambulatory blood pressure monitoring (ABPM). A computed tomography scan showed normal adrenal glands. Scintigraphy with DTPA (diethylenetriaminepentaacetic acid) labelled with technetium-99m radioisotope (^{99m}Tc-DTPA) did not show any foci of increased tracer uptake, neither in the adrenal glands, nor ectopically located. Doppler ultrasound of the renal arteries did not show any abnormalities. In repeated echocardiographic examinations no increase of heart cavities or wall thickness was found, and left ventricular mass index was within normal range. No features of hypertensive angiopathy were found in periodically repeated funduscopies. Despite changes in the hypotensive treatment regimen and a significant escalation of pharmacological treatment, there were difficulties in achieving normal BP values. Resistant hypertension was diagnosed. The patient reported

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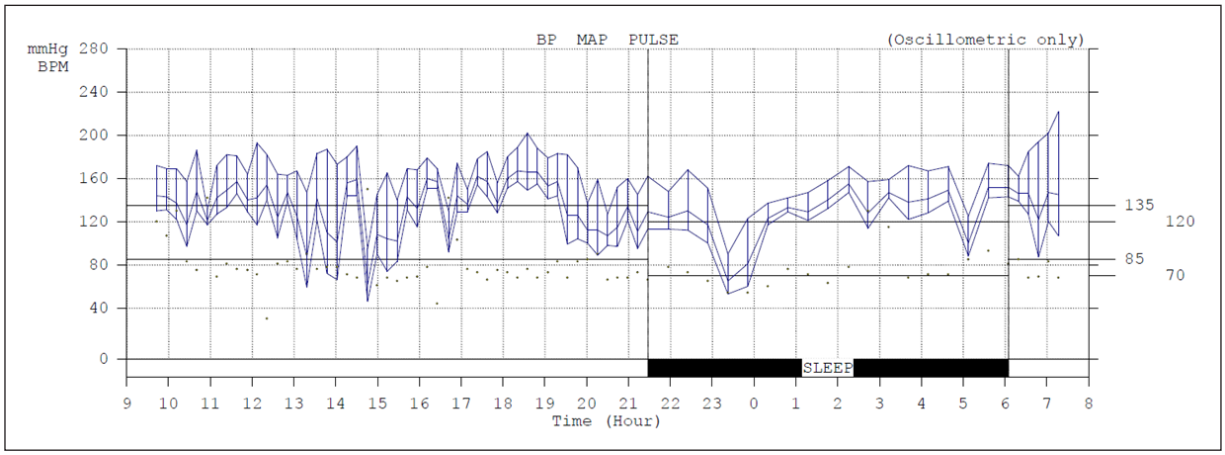

Figure 1. Ambulatory blood pressure monitoring — the examination was performed 4 days after the renal artery denervation surgery

frequent elevated BP values to over 220/140 mm Hg accompanied by palpitations and tachycardia in home measurements. This was frequently accompanied by severe nasal bleeding, which according to the patient was repeatedly treated by an ENT specialist with an anterior tamponade (no documentation was ever presented). Nineteen years earlier, chronic glomerulonephritis without impairment of renal excretory function had been diagnosed. Renal artery denervation was performed 9 years ago, after which no significant improvement in BP control was observed (Fig. 1).

On admission to the department, BP was 190/125 mm Hg. Recent hypotensive treatment: valsartan 320 mg in the morning, 160 mg in the evening, nitrendipine 2 × 20 mg in the morning and evening, indapamide 1 × 2.5 mg in the morning, torasemide 1 × 10 mg in the morning; spironolactone 1 × 100 mg at noon, metoprolol (succinate) 1 × 200 mg in the morning, doxazosin 4 mg in the morning and 8 mg in the evening; clonidine 3 × 0.15 mg, methyldopa 3 × 500 mg.

There were no significant abnormalities in laboratory tests. ECG showed sinus rhythm, regular, 80/min. There were no signs of left ventricular hypertrophy. Echocardiography showed only impaired left ventricular diastolic compliance. On abdominal ultrasound examination, normal kidneys of comparable size, with normal parenchymal and retroperitoneal differentiation were found, without signs of stasis and echoes of deposits over 0.3–0.4 cm. Other organs were also without any abnormalities. Doppler examination of the carotid and vertebral arteries showed unobstructed vessels with normal flow. *Intima-media* complex was bilaterally 0.6 mm. Doppler ultrasound of the renal arteries showed no abnormalities. The only noticeable change was high variability of heart rate depending on the body position: on the back about 72/min, on the right side about 90–95/min, on the left side up to 125/min.

During hospitalization, high BP was observed in traditional measurements and ABPM as well as sinus tachycardia up to 140/minute. In ABPM during the daytime activity period, the mean BP was 173/123 mm Hg, the maximum systolic pressure was 225 mm g and the minimum was 135 mm Hg. The maximum diastolic pressure was 158 mm Hg, the minimum was 86 mm Hg. During sleep, the mean blood pressure was 170/123 mm Hg, of which the maximum systolic pressure was 201 mm Hg, the minimum was 135 mmHg. The maximum diastolic pressure was 157 mm Hg, the minimum 71 mm Hg. The daily BP profile was defined as non-dipper — a nocturnal BP drop of 0.7% (Fig. 2).

Hypotensive treatment was intensified — the patient received: valsartan 2 × 320 mg in the morning and evening, nitrendipine 3 × 20 mg, indapamide 1 × 2.5mg, torasemide 1 × 20 mg in the morning, spironolactone 1 × 100 mg at noon, bisoprolol 2 × 10 mg, doxazosin 12 mg in the morning and 8mg in the evening, clonidine 3x 0.15 mg, isosorbide mononitrate 1 × 50 mg in the morning, methyldopa 3 × 500 mg.

After the medical staff implemented an additional regimen to control oral medication intake, a 2-day improvement in BP control was noted, with a reduction in blood pressure to below 130/80 mm Hg. In the following days, the mean daily blood pressure in traditional measurements was over 175/115 mm Hg. Tachycardia was also present despite high doses of beta-blocker. During the hospitalization, after the patient reported fast palpitations, ECG was performed several times, which

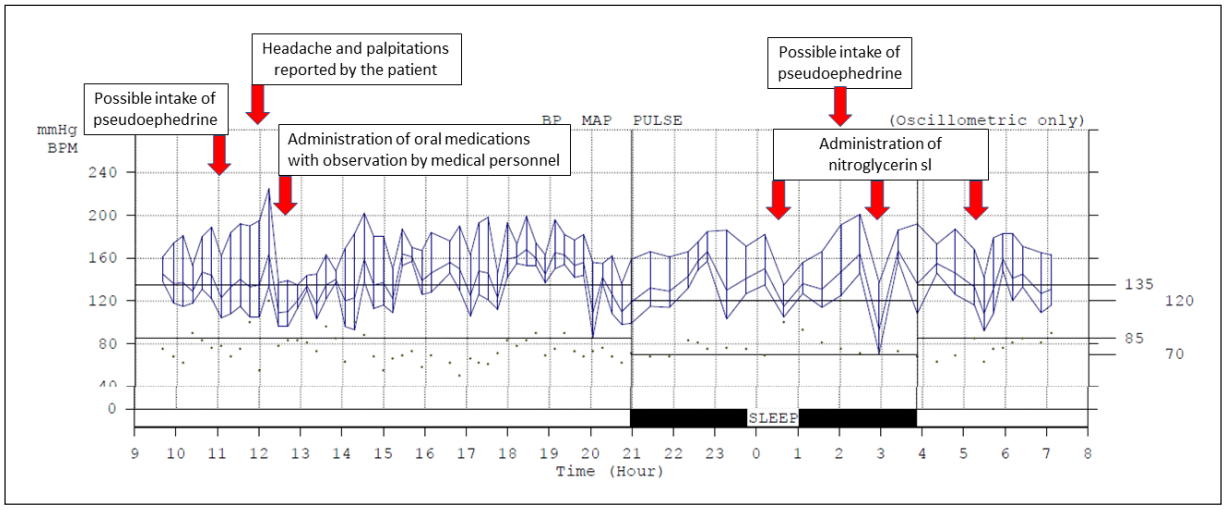

Figure 2. Ambulatory blood pressure monitoring — the examination was performed during hospitalization

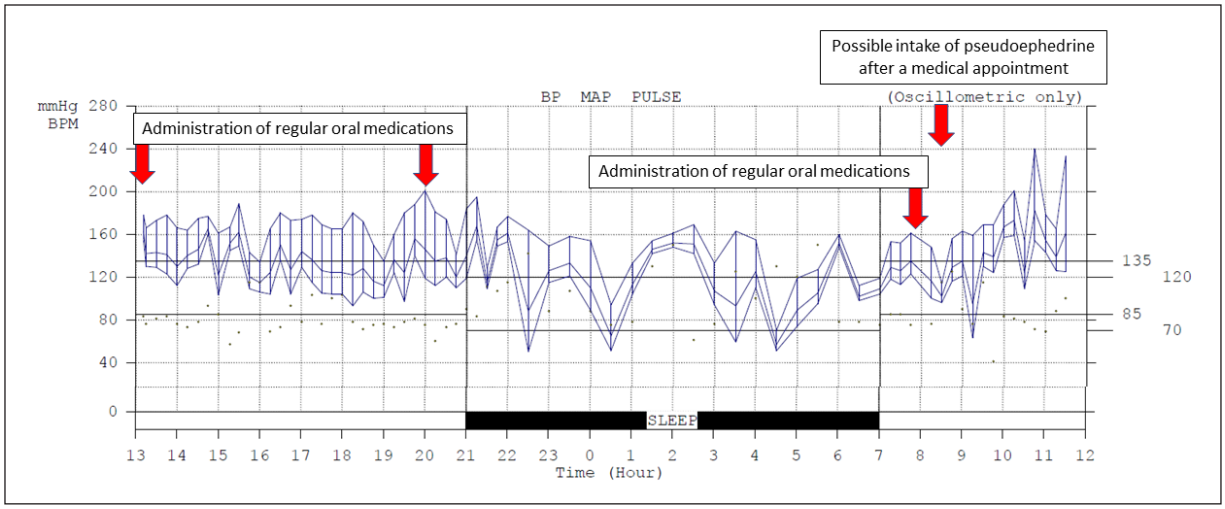

Figure 3. Ambulatory blood pressure monitoring — the second examination was performed during hospitalization

revealed an accelerated sinus rhythm without cardiac arrhythmia.

In the on-call reports, physicians noted a brief drop in BP after sublingual nitroglycerin administration (Fig. 3). Due to significantly elevated BP values, ECG monitoring and automatic blood pressure measurements every 15 minutes were initiated and drugs such as nitroglycerin, dihydralazine and urapidil were infused intravenously. Again, blood pressure normalization was achieved, but only during the first day of drug administration. Due to difficulties in maintaining patency and obtaining subsequent peripheral venous accesses, the central line was established to the right subclavian vein. On day 2, pneumothorax and subcutaneous emphysema developed and were treated with suction drainage for 5 days. Intentional manipulations and damage to intravenous lines by the patient could not be excluded. Moreover, massive nasal bleedings, requiring the placement of anterior tamponade, accompanied by markedly decreased haemoglobin concentration — about 1.5 mmol/l — occurred several times. Despite the frequent occurrence of similar nosebleeds at home, also immediately before admission to the clinic (according to the patient's report), in laboratory tests performed on admission, haemoglobin concentration was within normal limits, without features of erythrocyte renewal. According to the reports of patients who shared the same room, nasal bleedings always occurred after "nose cleaning with a stick or other object". During the bed rest regime and continuous ECG monitoring as well as continu-

ous automatic BP measurements, the lack of good BP control and periodic BP increases over 200/100 mm Hg were still observed.

During the hospitalization of the woman, the room she was lying in had to be changed. During the transfer, the attending physician's attention was drawn to a large number of pseudoephedrine cold tablets (over-the-counter) in the patient's possession. Due to still unclear causes of elevated BP and difficulties in lowering it, it was decided to perform tests to confirm the patient's use of hypotensive drugs and to search for substances increasing BP in the Department of Forensic Medicine. The test was performed by high-performance liquid chromatography (HPLC) — in the urine collected in the morning (about 2 hours after taking morning medication), during another episode of very high BP (approx. 220/120 mm Hg) accompanied by tachycardia (approx. 140/min), high urinary concentrations of pseudoephedrine and its metabolites were found, exceeding therapeutic concentrations twice and low concentrations of most hypotensive drugs inadequate to the doses used.

Pseudoephedrine is a sympathomimetic amine with peripheral effects similar to epinephrine and central effects similar to amphetamine. One of its side effects is precisely the increase in BP and tachycardia.

The patient was recommended for a psychiatric consultation, which did not take place during hospitalization. After a conversation with the patient in which the result of the toxicological examination was provided, the patient left the hospital at her request. Since then, the patient did not attend control visits in the hypertension outpatient clinic and was not hospitalized in the Clinic.

During the retrospective analysis of the case of this patient with a psychiatrist, Munchausen syndrome was suspected. It consists in deliberate, conscious production of symptoms of somatic or psychiatric diseases in order to obtain some medical services — diagnostics, therapy, care; the patient is not able to control the repeated, impulsive initiation of such behaviours, although they may sometimes lead to health- or life-threatening actions [1, 2]. Analysing previous medical histories, the fact was noted that some hospitalizations coincided with a change in the patient's living conditions; an entry was found in the documentation: "lives alone, separated from her partner". Perhaps, the escape into disease was to draw the attention of her closest environment to her health problems. During her stay in the ward, the patient had daily contact with her closest family members. No disturbed relations between the patient and her family were observed.

During previous hospitalizations, it was hypothesized that low *compliance* might be the cause of this patient's poor BP control. However, at that time no indication of intentional action of the patient raising BP was found. It was also pointed out that despite several years of resistant HT, no organ complications were found: normal glomerular filtration rate, no proteinuria/microalbuminuria, no signs of left ventricular hypertrophy on electrocardiography and echocardiography, normal *intima-media* complex thickness and no ocular fundus changes typical of hypertension were observed during each hospitalization. Transient improvement of BP control can be explained by special monitoring of oral medication intake. The deterioration of blood pressure control was probably related to the use of pseudoephedrine and possible vomiting provocation by the patient shortly after taking oral hypotensive drugs.

In the past, before "developing" hypertension, the patient was repeatedly hospitalized in the surgical wards due to recurrent abscesses of unknown aetiology in the right quadriceps, which required surgical treatment. The abscesses stopped appearing when during the next hospitalization in the same surgical ward the attending physician suspected that they were the result of the patient's conscious act and the patient was transferred to the psychiatry ward (Provincial Hospital for the Nervous and Mentally Ill in Gniezno).

The most common cause of pseudo-resistant HT is not taking hypotensive drugs. There are many circumstances that may arouse suspicion of poor cooperation between the patient and the doctor — the patient's failure to remember the names and doses of medicines taken, very infrequent visits to the doctor, good effect of medicines taken in the presence of medical staff, lack of characteristic symptoms of treatment with certain groups of drugs, for example, slowing down of heart rate with the use of beta-blockers, hypokalaemia after diuretics, and finally, the proceedings conducted to qualify for the receipt or extension of disability benefits [3–5].

Interactions of antihypertensive drugs with other chronically used drugs are also mentioned among the causes of ineffective hypotensive therapy [3].

Interactions with non-steroidal anti-inflammatory drugs (NSAIDs) are most commonly seen because of their over-the-counter availability and widespread use — they attenuate the hypotensive effect of all classes of antihypertensive drugs except calcium antagonists. NSAIDs cause sodium retention by inhibiting the vasodilatory and natriuretic effects of prostaglandins. Another group of drugs that weaken the hypotensive effect of most antihypertensive agents, cholestyr-

amine, thiazides, iron preparations and methyldopa through impaired absorption are drugs neutralizing the acidity of gastric juice. Accelerated hepatic metabolism, thus shortening duration of action or even complete inactivation of the drugs, is observed when using rifampicin and beta-blockers and calcium antagonists. There are indeed many drugs that may adversely modify the hypotensive effect, including preparations used in the pharmacological treatment of obesity, erythropoietin, tacrolimus, some immunosuppressants, oral contraceptives, anabolic steroids, sympathicomimetics such as abused nasal drops, corticosteroids, tricyclic antidepressants, and MAO inhibitors, taurine, amphetamine, methamphetamine, cocaine, caffeinated stimulants. However, it is important to remember that most of these interactions can be avoided if the treatment is planned correctly. Another problem is the use of herbal preparations, such as those with ginseng (an ingredient in preparations of energy boosters), or yohimbine (an ingredient in over-the-counter potency enhancers). It is also important to remember the pressor effect of glycyrrhizin, an active substance isolated from liquorice. Glycyrrhizinic acid (used as a sweetener in many herbal teas) and its metabolite glycyrrhetinic acid are potent inhibitors of 5-alpha-reductase and 5-beta-reductase and 11-beta-dehydrogenase, i.e. enzymes responsible for the degradation of adrenal steroids. Inhibition of the activity of these enzymes may result in decreased inactivation of steroids (cortisol), leading to increased concentrations of these hormones, as well as to a state of functional mineralocorticoid predominance (pseudoaldosteronism). Liquorice may therefore exacerbate hypertension, fluid retention, and hypokalaemia [3].

Cases of resistant hypertension in patients with Munchausen syndrome are described extremely rarely. An analysis of the PubMed database between 1995 and 2022 found 8 publications. Pessina et al. described the case of a young man who was diagnosed with hypertension in his teenage years. For many years, he complained of headaches, tachycardia, profuse sweating and significant increases in blood pressure accompanied by chest pain and temporary visual impairment, among other symptoms. Despite the administration of multi-drug hypotensive therapy at increasingly higher doses, his blood pressure values remained significantly elevated. Numerous diagnostic tests were performed — laboratory tests, ABPM, electrocardiography, echocardiography, Doppler ultrasound of the renal arteries, abdominal computed tomography, abdominal magnetic resonance imaging, coronarography, renal artery angiography, fundoscopy, microneurography, which excluded secondary forms of hypertension and did not confirm any organ complications of hypertension. Suspicion of exogenous substance-induced HT was raised. Amphetamine metabolites were detected in the patient's urine sample. After psychiatric consultation, Munchausen syndrome was diagnosed [6].

On the other hand, Zorzi described the case of a teenager with persistently high BP despite intensive hypotensive therapy. The patient was taking very high doses of caffeine orally. In his case a psychiatrist also made the diagnosis of Munchausen syndrome [7].

The article by Ponte et al. describes the case of a woman who came to the gynaecological emergency room, being 32 weeks pregnant. She also had persistently very high BP values despite complex hypotensive therapy. Due to lack of response to intravenous therapy, a caesarean section was performed at 36 weeks of gestation. In the following several months the woman was repeatedly hospitalised due to hypertensive episodes. All tests for secondary HT and organ complications were normal. Because of the diagnosed resistant HT and accompanying severe headaches and insomnia, which did not respond to analgesics, including opioids, the patient was referred to the psychiatric ward, where a diagnosis of Munchhausen syndrome was made, and the cause of the resistant hypertension were extremely high doses of caffeine [8].

Another interesting case is presented by Spitzer. He describes a 46-year-old nurse who was repeatedly hospitalised for hypertensive episodes with blood pressures reaching 300/150 mm Hg. She was repeatedly found to have elevated catecholamine levels, which would suggest a diagnosis of pheochromocytoma. Scintigraphy revealed an adrenal nodule and for this reason the patient was qualified for adrenalectomy. During the 6-month follow-up, normal blood pressure control was observed. However, after this period further uncontrollable increases in BP occurred. They were caused by vaginal administration of catecholamines (adrenaline, noradrenaline) [9].

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