MODERN PARACLINICAL EXPLORATION OF RENOVASCULAR ARTERIAL HYPERTENSION

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MODERN PARACLINICAL EXPLORATION OF RENOVASCULAR ARTERIAL HYPERTENSION (Abstract): Renovascular arterial hypertension (RVAHT) is a type of secondary arterial hypertension (considered the second one in terms of frequency in secondary AHT in adults), which is in a causality relation with a uni- or bilateral stenosis of the renal artery. The concept of RVAHT appeared with Goldblat’s experiments (1934), RVAHT being considered a clinical consequence of activation of the renin-angiotensin-aldosterone system. The prevalence of renal artery stenosis (RAS) increases with age, being seen in 7% of the individuals who are over 65 years old. Paraclinical investigations have the role to confirm the clinical suspicion (by objectifying the morphological lesion) and estimate the functional consequences of this lesion. Currently, many of these methods have maintained only their historical value, while in the forefront there are the non-invasive methods which allow a rapid and highly accurate diagnosis. Keywords: RENOVASCULAR ARTERIAL HYPERTENSION, RENAL ARTERY STENOSIS, RENIN.

Renovascular arterial hypertension (RVAHT) is a type of secondary arterial hypertension (considered the second one in terms of frequency in secondary AHT in adults), which is in a causality relation with a uni- or bilateral stenosis of the renal artery. The concept of RVAHT appeared with Goldblat’s experiments (1934), RVAHT being considered a clinical consequence of activation of the renin-angiotensin-aldosterone system (1-5).

The prevalence of renal artery stenosis (RAS) increases with age, being seen in 7% of the individuals who are over 65 years old. Renal artery stenosis is seen in 20% of the patients with coronary artery disease, 30% of those with aortoiliac disease and 50% of those with peripheral vascular disease. Classically, the accepted pathological criterion is that of “hemodynamically significant stenosis” (1, 2). The positive criterion is the reduction of the diameter by more than 60%, which corresponds to a reduction of the lumen area by about 85%. It is believed that a hemodynamically significant RAS –frequently contributes to the two major complications of the disease: causing renovascular arterial hypertension (RVAHT) and/or altering the renal parenchyma, structurally and functionally, with developing chronic renal failure. It must be remembered that a RAS of over 60% only
sometimes causes RVAHT and more commonly, but not necessarily, it causes renal ischemia with morpho-functional alteration (1, 7).

The causes of RAS can be systematized in the following manner:

1. **RENAL ARTERY ATHEROSCLEROSIS** (Renal artery stenosis through atheromatous plaque) – is the most common cause, it affects males, it appears in late ages; in this case, the stenosis is in the proximal third of the renal artery, sometimes associated with post-stenotic dilation; it can coexist with other stenosed vascular lesions (carotid lesions, lesions of the lower limb arteries).

2. **RENAL ARTERY FIBRODYSPLASIA**: it can present itself as medial fibro dysplasia, perimedial fibro dysplasia, intimal fibro dysplasia (more common in children), and subadventitial fibro dysplasia. Fibro dysplasia is more common in early ages, especially in women, and it usually affects 2/3 of the distal area of the renal arteries. They can also be seen in the context of collagen diseases (e.g., Marfan syndrome).

3. **RARE CAUSES**: renal artery thrombosis and embolism, arterial aneurysm, extrinsic compressions of the renal artery through tumors, arteriovenous fistula, abdominal aorta coarctation, Takayasu’s aortitis, renal artery hypoplasia, systemic vasculitis, neurofibromatosis, primary antiphospholipid syndrome, post-irradiation renal artery stenosis, cholesterol crystal micro embolism (1, 3-6, 11, 12).

The pathogenic mechanism of renovascular AHT mainly recognizes the activation of the renin-angiotensin-aldosterone system (experimentally described ever since 1934 by Goldblat), with particularities depending on the uni- or bilateral impairment of the renal artery (and, implicitly from the function of the contralateral kidney) (1, 5, 10).

The diagnosis of renovascular AHT obviously starts from a clinical suspicion which is based on the existence of some suggestive anamnestic or clinical elements. Starting from the criteria of Zanchetti issued in 2001, there are currently several clinical elements which, from a practical point of view, are indicating to the diagnosis of renovascular AHT (1, 11, 12, 14).

They can be represented by one or several of the following elements of clinical suspicion:
- Severe AHT in a child or young adult with no risk factors or after the age of 50 years;
- Severe AHT with onset at any age; onset of grade II severe hypertension (>160/100 mmHg in patients over 55 years old);
- Epigastric, subcostal or flank systolic/diastolic murmur;
- Short-time accelerated evolution of an AHT initially considered essential;
- AHT and inexplicable impairment of renal function;
- Relatively sudden deterioration of renal function in a hypertensive person;
- Refractory AHT in triple drug association;
- Deterioration of renal function as a response to treatment with ACE inhibitor;
- Extensive atherosclerotic lesions of the coronary, cerebral and peripheral arteries in a hypertensive person;
- Recurrent acute pulmonary edema apparently with no obvious cause;
- Lumbar pain with acute onset in the absence of urethral obstruction (1, 4, 5, 7, 9, 11, 12, 14).

Other elements which can orient the clinical suspicion are: the coexistence of
other cardiovascular risk factors: smoking, dyslipidemia, diabetes, worsening of renal failure under antihypertensive treatment, occurrence or worsening of renal failure after arterial catheterization, negative family history for hypertension, severe changes of fundus of eye in a hypertensive person.

There are also biological data which raise the suspicion of renovascular AHT:
- Hypokalemia;
- Hyponatremia;
- Increase of serum creatinine;
- High RA (renin-angiotensin);
- Moderate proteinuria;
- Increase of plasma renin.

Sometimes, a difference of more than 1.5 cm between the longitudinal diameters of the two kidneys in the echography examination, in the context of high BP values, can raise the suspicion of its renovascular etiology (imaging suspicion) (1, 4, 5, 7, 9, 11, 12, 14).

**PARACLINICAL INVESTIGATIONS** have the role to confirm the clinical suspicion (by objectifying the morphological lesion) and estimate the functional consequences of this lesion.

Currently, many of these methods have maintained only their historical value, while in the forefront there are the non-invasive methods which allow a rapid and highly accurate diagnosis.

Doppler examination of renal arteries combined with renal echography is a non-invasive, cheap method with high sensitivity and specificity, which can reveal the presence of renal artery stenosis (defined as the decrease of more than 60% of the renal artery diameter in the vascular duplex ultrasound) (7, 15 - 17). The method allows the anatomical and functional assessment of the renal arteries. Direct visualization of the main arteries is combined with measurement of the intrarenal pressure and velocity. The main drawback of this procedure is the lack of arterial visualization due to intestinal gases in 50-90% of the cases. At the same time, it allows to determine the resistive index at the level of the renal arteries which is usually high in the hypertensive patient in whom lesions of hypertensive nephron angiosclerosis occurred. The increase of maximum systolic velocity in the renal arteries >180 cm/s and a renal/aortic systolic velocity ratio >3.5 are suggestive of renal artery stenosis. A translesional systolic pressure gradient >15% may represent an indication for angioplasty (15-17). Duplex ultrasound also has a predictive value for the success of renal angioplasty; thus, if the resistive index in intrarenal circulation is higher than 0.8, it is considered that blood pressure will not return to normal after angioplasty in 97% of the patient, and in 80% of the subjects the renal function will not improve (18). However, Zeller et al. (19) have proven in a study on diabetic patients with severe stenosis of the renal arteries at the ostial level that favorable post-angioplasty results can be obtained even if this index exceeds 0.8. The main drawback of this procedure is sometimes the difficult visualization of the arteries due to intestinal gases in 50-90% of the cases.

Renal angiography by nuclear magnetic resonance (with gadolinium) allows the visualization of the renal arteries and accurately tracking renal artery stenosis, it has a high sensitivity and specificity, is non-invasive and potentially non-nephrotoxic. Its drawbacks are related to the need for the patient to maintain apnea during examination and the potential worsening of the results in the case of presence of intracor-
poral metallic bodies (stents, vascular clips, pacemakers) (fig. 1) (20-22).

Spiral computed tomography with CT angiography—entails contrast agent and irradiation of the patient. It has a good sensitivity and specificity for the diagnosis of renal artery stenosis, but it must be avoided in patients with severe chronic renal failure (7, 11, 12).

Selective renal arteriography is the gold standard to confirm the diagnosis. It is currently used in patients with high suspicion of renal artery stenosis in whom non-invasive explorations have been inconclusive. It also allows tracking of accessory renal arteries. The method helps establish the therapeutic indication: thus, concentric, unique critical stenosed (more than 75%) have indication of interventional treatment, while eccentric or multiple stenoses are directed to surgical approach. It has two important risks: nephrotoxicity of the contrast agent and the potential risk of renal atheroembolism. The limits are related to the lack of information regarding renal ischemia and the interdiction of use in significant renal failure (5, 7, 11, 12).

Analyzing 43 clinical cases explored by angiography in the Cardiology Department of "Sf. Spiridon" Hospital, result some practical conclusions. First, renovascular hypertension should be excluded before refractory hypertension is affirmed; 7 patients (16.2%) had this type of blood pressure profile in our analysis. Secondly, secondary hypertension is more frequent in young patients, but the atherosclerotic renovascular hypertension should be taken in account in patients older than 55 years (29 patients in our analysis – 67.4%) with acceleration of a pre-existing essential hypertension (8 patients – 18.6%). Thirdly, although duplex ultrasonography is recommended as the first-line imaging test to establish the diagnosis, the accuracy is operator dependent. When the clinical presentation is highly suggestive, digital subtractions angiography is the key method for both final diagnosis and endovascular treatment. If measuring the translesional pressure gradient to detect a functional artery stenosis is not available, selective bilateral renal vein renin measurement can be useful (19 patients had a significant ratio of 1.8-2) to decide revascularization. 31 of our patients had a successful endovascular revascularization (27 atherosclerotic lesions, 4 fibromuscular dysplasia lesions).

Fig.1. Right renal artery stenosis (collection from the Clinic of Cardiology)

Other methods: Renal isotopic scintigraphy, minuted intravenous urography – are rarely used in present day. Renal scintigraphy (infusion test after captopril) and other radio isotopic methods do not offer anatomic data. On the other hand, by clearly highlighting the infusion asymmetry, scintigram offers predictability data of curing AHT after revascularization, with a sensitivity of 75% and a specificity of 90%.
Scintigam cannot be interpreted in case of bilateral renal artery stenoses and cannot be applied in renal failure. Of the radio isotopic assessment methods of renal flow, those that use technetium-mertiotide or technetium-pentetic acid (DTPA) can determine, quite accurately, the fractional flow for each kidney. This very clearly suggests the possible ischemia, even in conditions of bilateral RAS. In the absence of any morphological information, radio isotopic explorations have not entered the routine practice (7).

The imaging methods will be completed by laboratory data:
- plasma renin activity (PRA) is increased by 50-80%;
- renin-captopril test has a sensitivity and specificity of 75-100%;
- determining plasma renin activity and especially the PRA ratio from the renal vein from the stenotic part and the PRA from the contralateral vein, comparing renin discharge from each kidney; it is useful to predict the success of a surgical revascularization. The increase of renin discharge from the ischemic kidney compared to the health kidney by 1.5 times is considered a positive test (1, 5, 7, 12).

**CONCLUSIONS**

We confirm that renovascular arterial hypertension continues to remain a challenge for the practitioner physician. The diagnosis is always based on the clinical suspicion and the combination of paraclinical investigations increases the sensitivity and specificity of the diagnosis. Of all methods, selective renal arteriography remains the gold standard of all paraclinical methods to confirm the diagnosis of renal artery stenosis.

**REFERENCES**

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Para phenyl diamine (PPD) is an aromatic amine derivative of Aniline that is widely used as a cosmetic product, particularly in hair dye preparations. PPD acute poisoning leads to respiratory distress, rhabdomyolysis, muscle necrosis and renal failure. Cardiac complications are rarely reported in the literature. We will present a case of PPD poisoning presenting as myocarditis, associated to rhabdomyolysis with a fatal outcome. The study presented the case of a 22-year-old man who was hospitalized for ingestion of a hair dye. At admission it had a severe edema of the face and neck. Laboratory exams showed renal failure, increased serum lactate dehydrogenase, creatine phosphokinase and troponine T. Toxicological screening showed the presence of Paraphenyl Diamine in blood and stomach. The patient died in the tenth day due to a cardiogenic shock. A forensic autopsy was performed. The pericardium was spotted by multiple hemorrhagic petechiae. The myocardium and the epicardium had multiple hemorrhagic areas. Histological examinations revealed the presence of acute inflammation of the myocardium and epicardium associated with severe ulceration of the endocardium. Inflammatory infiltrate consisted mainly of neutrophils with frequent micro abscesses in the myocardium and epicardium. Death was attributed to Paraphenyl Diamine poisoning complicated with rhabdomyolysis and acute myocarditis. In conclusion, PPD is often used as for suicidal attempt having acute toxic effects such as rhabdomyolysis with renal failure and respiratory distress. There is no specific antidote available in the management of the PPD poising (Jedidi M, Hadj MD, Masmoudi T, et al. Fatal toxic myocarditis induced by Paraphenylene Diamine. A case report. Rom J Leg Med 2016, 24(1): 17-20).

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