ADDED VALUE OF CATECHOLAMINE PHENOTYPING AND GENETIC SCREENING FOR THE CHARACTERIZATION OF PHEOCHROMOCYTOMA: A BELGIAN MULTICENTRE COHORT

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Objective: Pheochromocytomas/paragangliomas (PPGL) are rare neuroendocrine tumors arising from chromaffin cells of the adrenal medulla or from neural-crest derived sympathetic tissue. They secrete catecholamines in varying amounts, which accounts for their symptomatology. Hypertension is the most common sign, found in approximately 95% of patients. Nowadays, biochemical testing remains the simplest and most widely available method to assess PPGL in first intention. Identification of mutations in known susceptibility genes may help further refining tumor characterization and prognosis assessment. The objective of this study was to analyze clinical characteristics of PPGL from Belgium according to their secretory and genetic profiles.

Design and method: We retrospectively analyzed a cohort of 120 cases of non-syndromic PPGL diagnosed in 19 Belgian centres. Clinical characteristics were correlated with three catecholamine phenotypes based on urinary metanephrines (noradrenergic, adrenergic and silent) and with the results of genetic screening.

Results: Our cohort included a majority of women (59%). The mean age at diagnosis was 47±7 years. We documented the prevalence of pediatric (7.5%), extra-adrenal (13.3%), bilateral (2.9%), multifocal (5.1%), recurrent (8.5%), metastatic (7.6%) and familial (5.9%) cases. While the yield of positive genetic screening was low (15%), the presence of at least one of these criteria was associated with a 4-fold increased prevalence of mutation (30.3 vs 8.5%; p=0.03). In the subset in whom metanephrines values were available (n=62), the prevalence of adrenergic, noradrenergic and silent phenotypes was 58%, 34% and 8% respectively. Patients belonging to these three subsets differed by age at diagnosis (51±14; 38±17; 42±13 years; p=0.009), the proportion of extra-adrenal tumors (2.8%; 9.5%; 40%; p=0.016), pediatric (2.8%; 19%; 0%; p=0.074) and familial (0%; 18.8%; 0%; p=0.041) cases. Finally, an excess of dopamine secretion was associated with a higher prevalence of metastatic disease (25% vs 1.9%; p=0.005).

Conclusions: Secretory phenotypes and genetic profiles deserve to be integrated in the preoperative characterization of PPGL and may help orienting management and follow-up. Simple clinical features are associated with an increased probability of inherited tumor. Identification of an increased dopamine secretion should raise the suspicion of metastatic PPGL.

THE EFFECT OF THE MENSTRUAL CYCLE ON RENIN, ALDOSTERONE AND ALDOSTERONE-TO-RENIN RATIO IN FORMERLY PREECLAMPTIC AND HEALTHY WOMEN

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Objective: The aldosterone-to-renin ratio (ARR) is widely used as a screening test for primary aldosteronism (PA) in patients with hypertension. The purpose of the present original investigation is to identify the impact hormonal changes have on renin, aldosterone, and the ARR during the menstrual cycle of premenopausal women when measured in strict standardised conditions.

Design and method: We analysed 59 women with a history of preeclampsia and 6 healthy parous controls. Blood values were determined during both follicular and luteal phases of the menstrual cycle (days 1 and 14 respectively). Plasma aldosterone, active plasma renin concentration (APRC) and the ARR were measured under standardised conditions. All measurements were taken in the supine position at 9am, all patients maintained a standardised sodium diet (100 mmol/day) for no less than two weeks. In those who were receiving antihypertensive medications (n=2), all medications were discontinued at least 1 week prior to screening.

Results: When performing the Friedman's Test and the Wilcoxon signed rank test in formerly preeclamptic women (n=59), aldosterone and renin were both significantly elevated in the luteal phase (mean rank aldosterone 1.2 and 1.8 p0.000 Z-4.7, mean rank renin 1.23 and 1.77 p0.000 Z -4.5, respectively), however the ARR values did not significantly differ between phases (mean rank 1.53 and 1.47 p0.7 Z-0.14). When performing the Friendman's Test in the control group (n=6), the difference in aldosterone, renin and the ARR between the follicular and luteal phase was not significant (p0.059 for all parameters). Wilcoxon signed test revealed a significant difference in aldosterone (Z-2.02 p0.04), but the difference in renin and the ARR remained insignificant (p0.06).

Conclusions: In this study of premenopausal women we found that both renin and aldosterone are significantly affected by the menstrual cycle. However the resulting ARR was not statistically significantly altered. Our study indicates that it is not necessary to take the menstrual phase of patients into account when performing and interpreting the ARR as a screening test for PA in patients with a history of preeclampsia.

SUBTLE CORTISOL HYPERSECRETION IS ASSOCIATED WITH GLUCOSE HOMEOSTASIS AND INSULIN RESISTANCE IN NON-DIABETIC ESSENTIAL HYPERTENSIVE PATIENTS

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Objective: Patients with Cushing's syndrome (CS) and subclinical Cushing's syndrome (SCS) have a higher prevalence of cardiovascular complications than general population. Increased prevalence of impaired glucose tolerance has been reported in patients with SCS. Excess cortisol secretion can inhibit insulin secretion and impair insulin sensitivity and glucose uptake. We sought that a mild cortisol hypersecretion or an impairment in circadian cortisol rhythm might be associated with glucose homeostasis or insulin-resistance in essential hypertensive (EH) patients.

Design and method: In 155 non-diabetic EH patients we measured fasting glucose and insulin, calculated the HOMA-index, performed an oral glucose tolerance test (OGTT), calculated the area under the curve for glucose (GAUC) and insulin (IAUC), glucose level at 2-h of OGTT (G120), plasma cortisol level at 8 AM, 5 PM and 11 PM, and after overnight suppression with 1 mg of dexamethasone (DST), 24-h free urinary cortisol and plasma ACTH.

Results: GAUC and G120 were associated with both 11 PM and post-DST cortisol levels. Fasting insulin level, HOMA-index and IAUC were associated with post-DST cortisol level. These associations were independent of age, adiposity, plasma potassium and ACTH levels, alcohol intake and physical activity.

Conclusions: In non-diabetic EH patients free of overt CS or SCS, glucose uptake and insulin resistance are associated with subtle cortisol hypersecretion.

FOLLOW THE HEART OR THE GUT?

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Objective: This case underlines the importance of thoroughly investigating alternative causes for hypertension in patients with atypical presentations, regardless of their age and risk factors.

Design and method: Clinical case

Results: We present the case of a 68 year old woman without known cardiovascular diseases who came to the ER complaining of headaches, palpitations and chest pain of two hours duration. Upon admission, her blood pressure was 300/150 mmHg - overlapping values in all limbs with no asymmetric pulse. Heart rate was 140 bpm, rhythmic and without heart murmurs, abdomen without murmurs or palpable masses. Her ECG showed diffuse ST segment depression and high sensitivity troponin level at 0 h was 258 ng/L. Cardiac echo showed no wall motion abnormalities and no hypertrophy of the left ventricle. Her BP was acutely controlled with ACEi and iv nitroglycerin. Two hours after admission her BP returned to normal and remained within normal range without medication. Her ECG showed normal sinus rhythm with no other pathological findings. Coronary angiography was performed the next day and showed no atherosclerotic lesions. At this stage, her diagnosis was type 2 MI caused by severely elevated BP. Blood and urine tests revealed high levels of serum catecholamines and urinary normetanephrines - over 4000 micrograms/24 h. Abdominal ultrasound found a mass near her right kidney. Abdominal CT confirmed the presence of a nodular 5x3 cm mass in the right adrenal gland, compatible with a pheochromocytoma. She was submitted to laparoscopic adrenalectomy with normalization of her BP after the surgery. During follow-up, the patient presented with persistently normal blood pressure and normal ECG aspect without any chronic medication.

Conclusions: Pheochromocytoma is a rare neuroendocrine tumour originating in the adrenal gland medulla. Sustained or paroxysmal arterial hypertension is sometimes associated with the classic triad: episodic headaches, profuse sweating and tachycardia. A timely diagnosis and an effective therapeutic strategy are important, as this is a potentially fatal disease with a very good prognosis if discovered and treated early. It should be excluded in patients with high paroxysmal BP, especially if under 20 or over 50 years old.

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