THE GENETICS OF FAMILIAL ADRENAL TUMORS

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For a tumor type, the concept of «familial tumors» encompasses germline mutations predisposing either directly to this tumor, or to a syndrome to which the tumor type belongs. This general concept applies to adrenal tumors, and will be developed here. Adrenal tumors gather a broad range of diseases, scattered on two main categories depending on whether they are arising from adrenal cortex or medulla. From adrenal cortex, the dreadful adrenocortical carcinoma is in a large majority of cases sporadic and non syndromic. A germline mutation is found in less than 5% of cases, mainly related to Li Fraumeni syndrome (*TP53* mutations), or to Lynch syndrome (mutations in mismatch-repair genes). A vast majority of adrenocortical adenomas are sporadic, related to sporadic mutations — mainly *PRKACA* and *CTNNB1*. In terms of germline predisposition, adrenocortical adenomas seem more common in rare tumor predisposition syndromes such as Multiple Endocrine Neoplasia type 1 (mutations of *MENIN*) and Gardner syndrome (mutatons of *APC*). Primary macronodular adrenocortical hyperplasia is related to germline *ARMC5* mutations in $^1/_3$ of cases. Pigmented primary nodular adrenal dysplasia are often syndromic, part of the Carney complex (mutations of *PRKAR1A*). Other adrenocortical hyperplasias/dysplasias are rare, and several mutated genes have been reported. Tumors arising from adrenal medulla are called pheochromocytoma. These tumors are parented to paragangliomas, of extra-adrenal location. Approximately $^1/_3$ of pheochromocytoma and paragangliomas are related to germline mutations. The most commonly mutated genes are part of succinate deshydrogenase complex (mutations of *SDHB*, *C* and *D* mainly). Syndromic forms of pheochromocytoma include Multiple Endocrine Neoplasia type 2 (mutations of *RET*), Von-Hippel-Lindau syndrome (mutations of *VHL*) and neurofibromatosis type 1. Mutations in >10 other genes have been reported so far. An up-to-date catalogue of these mutations will be presented for each of this disease, with a special emphasis of their pathophysiological and clinical consequences.

KEYWORDS: familial adrenal tumors, genetics, mutations, multiple endocrine neoplasia.

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HYPERALDOSTERONISM

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Primary aldosteronism is the most common cause of secondary hypertension with the estimated prevalence of around 5—10% in hypertensive patients and up to 20% in those with refractory hypertension. However, it is still underdiagnosed in clinical practice. The disease is characterized by autonomous aldosterone overproduction, independent of renin-angiotensin system, which is caused by bilateral adrenal hyperplasia or aldosterone-producing adenoma in more than 90% of cases. Several studies have demonstrated that primary aldosteronism is associated with high cardiovascular, cerebrovascular and renal morbidity and mortality. Although hypokalemia is the hallmark of the disease, most of the patients are actually normokalemic. Recommended diagnostic evaluation involves measurement of plasma aldosterone and renin with subsequent calculation of aldosterone to renin ratio (ARR) which serves as the screening test for primary aldosteronism. In patients with elevated ARR this is followed by one of the four available confirmatory tests; oral salt loading, saline infusion, captopril challenge or fludrocortisone suppression test. If confirmatory testing is positive, further diagnostic investigations are directed toward identification of the primary aldosteronism subtype as the treatment differs between aldosterone producing adenoma and bilateral adrenal hyperplasia. Selective adrenal venous sampling for aldosterone is recommended as the only reliable way to separate unilateral from bilateral disease. Patients with unilateral disease are candidates for surgery whereas those with bilateral hyperplasia are treated with mineralocorticoid receptor antagonists. Early detection and appropriate treatment of primary aldosteronism could reduce morbidity and mortality to the levels seen in patients with essential hypertension.

KEYWORDS: hyperaldosteronism, secondary hypertension, aldosterone-producing adenoma, hypokalemia.

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MANAGEMENT OF PHEOCHROMOCYTOMA

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The report focuses on catecholamine-secreting tumors that develop from chromaffin cells of adrenal medulla and sympathetic ganglia, which are referred to as pheochromocytomas and catecholamine-secreting paragangliomas. Catecholamine-secreting tumors are rare, with an annual incidence of two to eight cases per a million people. There are 6—8% of pheochromocytomas among incidentally discovered adrenal tumors. Nevertheless, it is important to suspect, confirm, localize, and remove these tumors because associated hypertension is treated with surgical removal of a tumor. There is mortality risk (especially when the diagnosis is unknown). At least 5—6% of tumors are malignant; up to 30—35% of tumors are familial. Thus, detection of these tumors in the proband may result in early diagnosis in other family members. The report summarizes epidemiological data; pathogenesis; laboratory, genetic and topical diagnostic

options of chromaffin tumors. It emphasizes important aspects of preparing for surgery, and discusses prognosis.

KEYWORDS: pheochromocytoma, adrenal tumors, hypertension, management.

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THYROID DISORDERS ASSOCIATED WITH IODINE DEFICIENCY IN PRACTICE OF ENDOCRINOLOGISTS

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Iodine deficiency (ID) impairs thyroid hormone production and has many adverse effects throughout the human life cycle. The most serious effect of ID is mental impairment in children, adolescents and adults. Goiter is the most visible and well known effect of insufficient iodine nutrition. Management of goiter and other thyroid disorders caused by ID is an important part of routine clinical practice of endocrinologists. Moreover, in dealing with thyroid disorders the clinicians should be well aware of changing patterns of iodine intake to make necessary amendments to their clinical practices. Effective goiter prevention program (combination of massive use of iodized salt and distribution of iodine supplements in vulnerable groups of population) was conducted in the USSR until 1990 and reduced goiter prevalence to nearly sporadic level. Collapse of iodized salt production in 1991—1992 led to a significant increase in goiter morbidity, especially in areas with severe ID. It took nearly half decade before this negative trend had been realized and another 10 years or more before situation had improved in the former USSR countries that had adopted universal salt iodization (USI) strategy. However, this progress has been much less spectacular in Russia and Ukraine that are still relying only on a voluntary use of iodized salt. In Russia, certain regions (Moscow, Tyumen, St.-Petersburg) with move advanced voluntary salt iodization programs may have median UIC in children in the optimum range (100—300 mcg/l). In other regions and, especially, in rural areas ID still remains widespread. Several sub-national surveys conducted in Russia regions (oblasts) in the past 10—15 years showed mild-to-moderate ID (median UIC in the range of 40 to 80 mcg/l). This uneven pattern of iodine nutrition provides another challenge to endocrinologists who should adapt their clinical strategy in dealing with thyroid disorders to potential status of iodine deficiency (or sufficiency) in the given territory. Thus, major benefits of increasing iodine intake though salt iodization in populations with mild-to-moderate ID are decrease in prevalence of goiter, thyroid autonomy and thyrotoxicosis in adults and increase in IQ in children. In the situation of optimum iodine nutrition populations, especially children, are better protected from radioactive iodine exposure in case of nuclear accident. These benefits occur at the expense of a small increase in the prevalence of subclinical hypothyroidism in adults that could be minimized by avoiding excessive iodine intakes.

KEYWORDS: iodine deficiency; goitre; universal salt iodization.

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THYROID CANCERS: THE STATE OF THE ART MANAGEMENT

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Thyroid nodules are a common clinical problem, and differentiated thyroid cancer (DTC) is becoming increasingly prevalent. High-resolution ultrasound can detect thyroid nodules in 20—70% of randomly selected individuals, with higher frequencies in the elderly. The main clinical problems concerning thyroid nodules are US-based categorization of the malignancy risk and indications for US-guided fine-needle aspiration biopsy (FNA), cytological classification of FNA samples, the roles of immunocytochemistry and molecular testing applied to thyroid FNA, therapeutic options, and follow-up strategy. Recent advances in research on thyroid carcinogenesis have yielded applications of diagnostic molecular biomarkers and profiling panels in the management of thyroid nodules. Differentiated thyroid cancer (DTC), which includes papillary and follicular variants, comprises the vast majority (>90%) of all thyroid cancers. Most of the detected tumours are very small and have unknown clinical importance and malignant potential. 25% of the new thyroid cancers diagnosed in 1988—1989 were less than 1 cm compared with 40% of the new thyroid cancer diagnoses in 2008—2009. This tumour shift can be explained due to the increasing use of neck ultrasonography or other imaging very often without clear clinical indications and switch last clinical recommendations to less aggressive initial treatment with organ-saving in patients with thyroid microcarcinomas. Nevertheless clinical controversy still exists in many areas of thyroid cancer management. The management of very rare medullary thyroid cancer is now generally based on molecular testing of RET-proto-oncogen mutations. The main directions for further research in the field of thyroid cancer and nodules are optimizing molecular markers for diagnosis, prognosis, and therapeutic targets, improvement of the risk stratification and understanding of the risks and benefits of DTC initial treatment options.

KEYWORDS: thyroid nodules, differentiated thyroid cancer, fine-needle aspiration biopsy.

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GRAVES' DISEASE

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Graves' disease is an autoimmune disease where activating thyroid-hormone receptor antibodies cause thy-