Editorial: The adrenal gland: central relay in health and disease

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MAIN TEXT

INTRODUCTION

Diseases of the adrenal gland are as important for the general practitioner as for the endocrine specialist. The high prevalence of some adrenal endocrinopathies, such as adrenal incidentalomas (1-2% of the population) and primary aldosteronism (6% of hypertensives), which affect millions of patients, makes adrenal diseases such a relevant health issue. The high morbidity and mortality of some of the rarer adrenal diseases, i.e. Addison's disease and Cushing's syndrome (Table 1), make early detection and appropriate treatment such a challenge for the health care system.

Progress in genomics, transcriptomics and steroidobolomics has advanced our understanding of adrenal pathologies including primary aldosteronism [1], Cushing's syndrome [2], adrenocortical carcinoma [3], and pheochromocytoma [4]. Recent progress has been made in the pathophysiology of many rare adrenal diseases. Foremost has been the identification of somatic driver mutations in adrenal cortical neoplasms responsible for the characteristic endocrine autonomy and limited proliferative activity of these endocrine tumors [1]. The rich genetic background of neoplasms derived from adrenal and extra-adrenal chromaffin cells is well established with over 16 germline mutation identified to date, many of these and other (HIF2a, IDH1 & 2, HRAS) also contributing via somatic driver events [4]. It is within this horizon that adrenal diseases have become a general topic in research and in clinics.

THE ADRENAL CORTEX CONFERENCE IN MUNICH 2018

In June 2018, we had the privilege to organize the 18th Adrenal Cortex Conference in Munich. Since 1984 the Conference on the Adrenal Cortex has provided an exciting combination of

science and resources for basic and clinical scientists. The 2018 conference continued the tradition of including renowned speakers covering the latest research on adrenal development, hormone signaling, steroidogenesis, adrenal insufficiency, primary aldosteronism, Cushing's syndrome and adrenal cancer. As in previous meetings, the Keith L. Parker Memorial Lecture was awarded to an international leader for his or her contribution to adrenal research. This year's laureate was William E. Rainey, the Jerome W. Conn Professor at the University of Michigan, Ann Arbor, USA, who presented a lecture on his most recent research on the molecular pathophysiology of primary aldosteronism. Two hundred scientists from around the globe participated in this prime event of adrenal research giving the meeting a truly international flavor. More than 100 investigators including many students and young post-docs presented their research as posters or oral communications.

We acknowledge the generous support of the Deutsche Forschungsgemeinschaft, which enabled us to invite many of the internationally leading researchers in the field. Furthermore, the present December volume of Experimental and Clinical Endocrinology and Diabetes is entirely dedicated to reviews covering advances in the field of primary aldosteronism. They are written by experts in their respective fields and include twelve invited articles summarizing main topics covered at the symposium.

Primary aldosteronism (PA) has been identified as the leading endocrine cause of hypertension in recent years. Although still utterly underdiagnosed in clinical practice recent data point to a higher detection rate in some countries. PA is easily picked up if screened by the aldosterone-to-renin ratio. However, there are many factors influencing sensitivity and specificity of the ratio, an area explored by the review of Schilbach, et al. [5]. Perez-Rivas et al. [6] cover in their review on familial hyperaldosteronism the most recent genetic findings

currently leading to a potential reclassification. Although there has been a debate about the true prevalence, with estimates up to 6% in systematic screening approaches [7], genetically confirmed familial hyperaldosteronism remains a quite rare entity affecting less than 1% of diagnosed cases of primary aldosteronism. Usually, affected patients present early in infancy and have a severe course of the disease. Yang et al. [8] provide an analysis of the outcome of adrenalectomy in unilateral primary aldosteronism. Based on a recently established expert consensus of 31 specialists, assessment of outcome has been standardized allowing improved comparison between cohorts of different geographic and genetic backgrounds [9]. However, this analysis also demonstrated that a certain percentage of patients have in biochemical terms persistent hyperaldosteronism, and the underlying pathophysiology is discussed in this review.

Two manuscripts review the recent advances in the treatment of malignant adrenal diseases, namely adrenocortical carcinoma (ACC) and malignant pheochromocytoma/paraganglioma (PPGL). A major breakthrough in treatment of adrenocortical carcinoma has been the FIRMACT trial published in 2012 [10] which reported results of a randomized trial comparing 2 chemotherapeutic regimens in stage IV ACC. As a result of this trial, multiple second and third line therapies have been evaluated [11] which are reported in the review article by Megerle et al. [12]. Approximately 10% of all PPGL are malignant, and treatment options in metastasized disease stages include radioactive treatment options (MIBG, somatostatin receptor based approaches), classical chemotherapy protocols and targeted treatment approaches. Nölting et al. [12] provide a comprehensive overview of the most recent advances in the field, including promising pre-clinical data not yet used in clinical practice.

Erlic and Beuschlein [13] summarize the metabolic alterations found in PPGL, including impaired glucose homeostasis and lipolysis activation, changes in body weight, fat mass and distribution. Schreiner et al. cover the highly relevant topic of perioperative management of adrenal tumors [14]. In clinical practice this area is associated with serious morbidity and mortality which can be avoided by appropriate management.

Cushing disease (CD), caused by corticotroph adenomas of the pituitary, is a rare devastating disease with high clinical burden. Remission by transsphenoidal adenomectomy is achieved in 78% [15], but often metabolic, cardiovascular, musculoskeletal and psychiatric comorbidities persist after long-term biochemical control. These chronically ill patients show an increased mortality despite disease remission. According to the review by Stalla et al. [16], comorbidities should be treated aggressively and life-long surveillance is necessary to identify tumor recurrence at an early stage. Kamilaris et al. [17] give an excellent overview of genetics and clinics of primary pigmented nodular adrenal disease, a rare cause of adrenal Cushing's syndrome, often associated with additional syndromatic features.

This special issue also highlights the importance of non-tumorous adrenal diseases with high morbidity, such as Addison's disease (AD) and congenital adrenal hyperplasia (CAH). In a timely review, Barthel et al. [18] reflect upon current treatment standards in AD and improvements in long-term care. Reisch [19] summarizes the long-term sequelae observed in patients with CAH. There is a shift from the pediatric focus on management of adrenal crisis and growth to adult problems, namely reproduction and prevention of long-term cardiovascular and metabolic consequences of the disease.

The final manuscript by Di Dalmazi [20] addresses recent progress in adrenal incidentalomas, a topic which has been covered by a European guideline in 2016 [3]. In clinical practice these guidelines have proven to be very helpful. However, as in other areas of adrenal research, many open questions remain and have to be addressed by future studies.

It is within this context that the recently established clinical research center (CRC), "The adrenal gland: central relay in health and disease" [21], is well suited to approach clinical issues and basic research questions. The Deutsche Forschungsgemeinschaft approved funding for this program with 13 mio € from 2017 to 2021, with the option of a further extension until 2029. The 17 research projects and two central support projects at the University Hospitals of Dresden, Munich and Würzburg cover a broad spectrum ranging from sepsis research to Cushing's syndrome, and adrenal gland organ replacement to rodent models of autoimmune adrenal disease. Several of its principal investigators of the CRC are authors of reviews of this special issue. Other authors are close collaborators of the CRC scientists, reflecting its international outreach. This special issue of Experimental and Clinical Endocrinology and Diabetes provides the interested reader with an opportunity to understand where we are, and where our research has to go until the next Adrenal Cortex Conference in 2020.

DECLARATION OF INTEREST

The authors declare no conflict of interest.

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Table 1: Incidence and prevalence of adrenal diseases in Europe. N.k., not known; OR, Odds ratio; EH; essential hypertension; PA, primary aldosteronism; IAH, idiopathic adrenal hyperplasia; CD, Cushing disease; SMR, standard mortality rate;

	Annual incidence	Prevalence	Morbidity	Mortality
Congenital adrenal hyperplasia	1:10.000 – 1:15.000		5.8 crises per 100 patient-years; salt wasting: 8.8; simple virilising: 2.5	The HR of dying 2.3 (95% CI, 1.2– 4.3) in CAH males and 3.5 (95% CI, 2.0 – 6.0) in CAH females compared with controls
Addison's disease	4.5/1000.000	82-144/ 1000.000	6-8 adrenal crisis/ 100 patients/year	0.5 deaths/100 patient-years from adrenal crisis
Primary aldosteronism	n.k.	4-6% of hypertensive population	OR for stroke: 4.2; OR for mi: 6.5; OR for AF: 12.1 compared to EH	2 times increased for treated PA (IAH)
Cushing disease	1-3/1000.000	66/1000.000		SMR for all-cause mortality in treated CD: 1·61
Incidentally detected adrenal mass	n.k.	1-2% of general population	n.k.	n.k.
Adrenocortical carcinoma	0.7 – 2.0/ 1.000.000			Median survival: 3-4 years, 5-year survival 60–80% for localized tumors, and 10-20% for metastatic disease