CHAPTER 10

Adrenal Tumors in MEN1 Syndrome and the Role of Menin in Adrenal Tumorigenesis

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Introduction

Most of the adrenal tumors are benign adrenocortical adenoma (AA) and pheochromocytomas (Pheo) originating from the adrenal medulla, but rarely malignant adrenocortical carcinomas (ACC) can be also found. Adrenal tumors causing hormonal overproduction such as aldosterone-producing and cortisol-producing tumors are also rare, whereas nonhyperfunctioning adenomas occur more frequently.[1] During the last decades an extensive use of advanced imaging techniques (computer tomography, magnetic resonance imaging, endoscopic ultrasound) has led to an increased incidence of accidentally discovered adrenal masses, i.e., incidentalomas.[2-4] The prevalence of incidentalomas is up to 9% of all autopsy cases. The majority of these tumors are hormonally inactive and are of adrenocortical origin, but pheochromocytomas and hormonally active adrenocortical tumors associated with the development of Cushing's syndrome or primary aldosteronism can also be found in some patient.[1,4]

Several clinical studies provided compelling evidence that adrenal tumors are associated with MEN1 syndrome and that patients with MEN1 syndrome may develop the entire spectrum of adrenal tumors including nonhyperfunctioning adenomas, cortisol- and aldosterone-producing tumors, adrenocortical carcinomas and, rarely, pheochromocytomas. However, adrenal tumors are not included in the main diagnostic components of MEN1 syndrome and patients with adrenal tumors who have only one of the three components without family history of MEN1 usually do not have mutations of the *MEN1* gene. Perhaps more interestingly, the somatic genetic alterations detected in MEN1-associated adrenal tumors do not seem to support a role for *MEN1* gene similar to that presumably involved in the pathomechanism of MEN1-associated parathyroid, pituitary or pancreas neuroendocrine tumors.

Genetics of Adrenal Tumors

Hereditary adrenocortical tumors are rare, but up to 25-30% of pheochromocytomas are associated with hereditary syndromes.[5,6]

Hereditary Syndromes with Adrenal Involvement

Hereditary adrenocortical tumors represent only a few percent of all adrenal tumors. In Li-Fraumeni syndrome (LFS; OMIM 151623), germline mutation of the tumorsuppressor gene

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Table 1. Genetics of adrenal tumors. Hereditary tumor syndromes associated with adrenal tumors

	Gene and Chromosomal Localization	Tumors and Other Manifestations
Li-Fraumeni syndrome	*TP53* (17q13)	ACC, breast cancers, brain tumors, soft tissue sarcoma leukaemia
Multiple endocrine neoplasia Type 1 (MEN1)	*MEN1* (11q13)	3P: Parathyroid, pituitary, pancreas tumors; adrenal cortical; adenoma, hyperplasia, rarely carcinoma
Carney complex (CNC)	*PRKARIA* (17q22-24) *PDE11A* (2p16)	PPNAD, cardiac myxomas, GH- and PRL-secreting tumors, thyroid tumors, testicular tumors, ovarian cysts, lentiginosis,
Beckwith-Wiedemann syndrome (BWS)	*11p15* locus alterations *IGF-II* overexpression	Omphalocele, macroglossia, macrosomia, hemihypertrophy, Wilms' tumor, ACC
Congenital adrenal hyperplasia (CAH)	*CYP21A2* (6p)	Adrenal hyperplasia
Glucocorticoid-remediable aldosteronism (GRA)	*CYP11B1* (8q21) *CYP11B2* (8q21)	Micronodular, homogeneous hyperplasia

ACC: adrenocortical cancer; ADE: adrenocortical benign adenoma; GH: growth hormone; PRL: prolactin; IGF: insulin-like growth factor; GRA: Glucocorticoid-remediable aldosteronism.

TP53 can be identified,[7,8] whereas in Beckwith-Wiedemann syndrome (BWS; OMIM130650) overexpression of the insulin-like growth factor-2 (IGF-2) can be detected.[5] Mutations of the protein kinase A regulatory subunit-1α (*PRKAR1A*) gene have been associated with Carney complex (CNC; OMIM 160980).[9,10] In addition, mutation of the gene encoding the phosphodiesterase 11A enzyme (*PDE11A*) has been reported recently in patients with micronodular adrenocortical hyperplasia.[11] Multiple endocrine neoplasia Type 1 (MEN1; OMIM 131100) syndrome has been associated with mutations of the *MEN1* gene.[12] Glucocorticoid remediable hyperaldosteronism (GRA) is caused by a chimeric gene containing the promoter region of the *CYP11B1* (OMIM 610613) gene and the coding sequence of the *CYP11B2* gene (OMIM 12408) (Table 1).[13] Congenital adrenal hyperplasia is caused by mutations of the *CYP21A2* (*CYP21B*; OMIM 201910).[14,15] Activating mutations of the alpha chain of the stimulatory G protein have been described in McCune-Albright syndrome (MAS; OMIM 174800), but in this case somatic mosaicism occurs.[16]

Somatic Genomics of Sporadic Adrenal Tumors

Different molecular biological techniques, such as comparative genomic hybridization (CGH) and microsatellite analysis have been used in genome-wide screening for the identification of additional loci involved in adrenal tumorigenesis. Using CGH, chromosomal alterations have been observed in 28-61% of adrenal adenomas. Hot-spots for allelic losses have been identified on chromosomes 1p, 2q, 11q, 17p, 22p and 22q and gains on chromosomes 4, 5, 12 and 19.[17] Kjellman et al (1999) screened a panel of 60 tumors (39 carcinomas and 21 adenomas) for loss of heterozygosity (LOH). The vast majority of LOH detected was in the carcinomas involving chromosomes 2, 4, 11 and 18; but little was found in the adenomas. The Carney complex (160980) and the *MEN1* loci on 2p16 and 11q13, respectively, were further studied in 27 (13 carcinomas

and 14 adenomas) of the 60 tumors. A detailed analysis of the 2p16 region mapped a minimal area of overlapping deletions to a 1-cM region that was separate from the Carney complex locus. LOH for glycogen phosphorylase gene (PYGM, OMIM 608455) was detected in all 8 informative carcinomas and in 2 of the 14 adenomas. Of the cases analyzed in detail, 13 of the 27 adrenal tumors (11 carcinomas and 2 adenomas) showed LOH on chromosome 11 and these were selected for *MEN1* mutation analysis. In 6 cases a common polymorphism was found, but no mutation was detected. The authors concluded that LOH in 2p16 was strongly associated with the malignant phenotype. In addition, LOH in 11q13 occurred frequently in carcinomas, but it was not associated with *MEN1* mutations, suggesting the involvement of a different tumor suppressor gene on this chromosome.[18]

Studies using microsatellite markers have demonstrated high percentages of loss of heterozygosity (LOH)/allelic imbalance at region 11q13 (in 100% of cases)[19-21] and 2p16 (in 92% of cases)[18] in adrenal carcinomas. LOH of the 17p13 locus has been reported to be highly specific to malignant tumors[22] and to be of prognostic value for the recurrence of localized tumors.[23] Based on these findings LOH at 11q13 occurs in about 20% of sporadic adrenal tumors, mostly in benign adrenocortical adenomas and in up to 40% of patients from MEN1 kindreds.[17-24]

Unlike the LOH at 11q13 detected in adrenal tumors, somatic mutations of the *MEN1* gene are very rare. Two studies conducted mutation screening of the *MEN1* gene. Heppner et al (1999) found no mutations within the coding region of the *MEN1* gene in 33 tumors and cell lines.[20] Schulte et al (1999) studied 16 patients with sporadic adrenal adenomas (4 patients had incidentally discovered masses, 5 patients had primary aldosteronism, 6 patients had Cushing's syndrome and one patient had multinodular hyperplasia) and only one patient with hormonally inactive adrenal adenoma showed a heterozygous missense mutation (Thr552Ser).[21] Retention of heterozygosity for the *MEN1* locus at 11q13 was also observed by Skogseid et al (1992), who analysed adrenocortical lesions in 31 MEN1 patients. Of the 31 patients, 12 (37%) had adrenal enlargement, which was bilateral in 7 patients. Of the 12 adrenal lesions 11 were benign adenomas and all retained heterozygosity for the *MEN1* locus. One interesting clinical observation on the association between adrenal and pancreatic endocrine tumors has been reported. In a single adrenocortical carcinoma, loss heterozygosity for alleles at 17p, 13q, 11p and 11q has been identified, which is in agreement with reports in sporadic cases. Skogseid et al (1992) concluded that the pituitary-independent adrenocortical proliferation is not the manifestation of a primary lesion in MEN I but it may represent a secondary phenomenon, perhaps related to the pancreatic endocrine tumor.[25]

MEN1-Associated Adrenal Tumors

Individuals who have a germline inactivating mutation of the *MEN1* gene develop MEN1 syndrome. In accordance with Knudson's two-hit hypothesis, their germline *MEN1* mutation combines with acquired somatic mutations of the second copy of their *MEN1* gene. This leads to monoclonal expansion and multiple neoplasia arises in such organs as the pituitary, parathyroid glands and the endocrine pancreas in an autosomal dominant manner.[26,27]

Prevalence

In the first family described by Wermer peptic ulcer and tumors of the anterior pituitary gland, parathyroid glands and islets of Langerhans, adenomas of the thyroid and of the adrenal cortex, as well as lipomas were identified.[28,29] In the past 50 years the prevalence of adrenal lesions observed in *MEN1* mutation carriers varied between 8 to 73% (Table 2.).[25,30-37]

Clinical Features

Similar to the usual presentation of sporadic adrenocortical tumors, adrenal cortical adenomas found in MEN1 usually are hormonally inactive but in a proportion <10% cortisol-secreting tumors can be found. Primary aldosteronism has also been occasionally reported.[38,39] Adrenocortical carcinomas (ACC) has been described only in a few cases and pheochromocytomas may occur in less than 1% of MEN1 patients.[32,33,40]

Table 2. Prevalence of the adrenal tumor in multiple endocrine neoplasia Type 1 (MEN1) among the MEN1 mutation carriers

Country of Origin	Number of Patients with Adrenal Tumor	Number of Total Mutation Carriers	Prevalence	Reference
Finland	29	82	35%	Vierimaa O et al
UK	5	59	8%	Ellard S et al
Germany (a multicenter study)	38	258	15%	Machens A et al
Germany	21	38	55%	Waldmann J et al
France	15	62	24%	Giraud S et al
Sweden	12	33	37%	Skogseid B et al
Hungary	1	10	10%	Balogh K et al
Germany (2008, EUS)	36	49	73%*	Schaefer S et al

*including plump adrenals.

Diagnosis, Therapy and Follow-Up of Adrenal Tumors

Localization

Most adrenal tumors found in patients with MEN1 syndrome are small, benign, hormonally inactive adrenocortical adenomas. These tumors are mostly discovered by routine imaging techniques, i.e., ultrasonography, CT or endoscopic ultrasound (EUS).[2,37] The sensitivity of EUS in the detection of adrenal lesions in MEN1 is higher than that observed with CT. Schaefer et al reported a very high percentage (73%) of patients with adrenal involvement among *MEN1* gene mutation carriers.[37] However, we should keep in mind that in this particular study all the EUS were performed by a single investigator who was searching for adrenal lesions. In routine clinical practice this high sensitivity could be difficult to reproduce when different investigators are doing the EUS examinations.[37]

Pheochromocytoma does not represent a major MEN1 manifestation, however, it can be observed in <1% of patients. 131I-MIBG (meta-iodo-benzyl guanidine) scintigraphy is a highly specific imaging technique for the diagnosis of pheochromocytoma.[41,42]

Laboratory Diagnosis

Although adrenal lesions in patients with MEN1 syndrome are mostly hormonally inactive adenomas, hormone secretion should be excluded. Urinary cortisol, midnight serum and salivary cortisol and the low-dose dexamethasone suppression test can be applied for the diagnosis of Cushing's syndrome. The plasma renin/aldosterone ratio is used for screening primary aldosteronism and adrenal androgens should also be determined.

In case of clinical suspicion of pheochromocytoma, urinary catecholamine metabolites (metanephrine, normetanephrine, homovanillic acid, vanillylmandelic acid) and serum chromogranin A determinations should be performed.[43]

Therapy

The therapeutical procedures for patients with MEN1-associated adrenal tumors are similar to patients with the sporadic counterparts. All functioning adrenal tumors and nonfunctioning tumors larger than 4 cm with evidence or suspicion of malignancy should be surgically resected. Nonfunctioning adrenal tumors smaller than 4 cm should be evaluated using imaging techniques and hormone measurements. Based on CT scan lipid-rich and lipid-poor tumor can be identified. If lipid-rich tumor is observed, imaging should be repeated after 6 month, while in cases when

lipid-poor tumor is observed repeat CT or MRI is indicated after 3 months. If enlargement occurs adrenalectomy should be considered. In addition, adrenalectomy should be considered when heterogeneity, irregular capsule, nodes or change in hormonal activity are observed.[44,45]

Follow-Up

The main manifestations, pituitary adenomas, parathyroid hyperplasias causing primary hyperparathyroidism and pancreatic endocrine tumors are the major prognostic factors for the long-time survival of patients with MEN1. Primary treatment and additional work-up for these conditions can be found in Chapter 1 of this book.

Long-term follow-up for detection of adrenal tumors in MEN1 mutation carriers includes imaging studies and, if necessary, hormone measurements. An extensive use of imaging techniques, especially EUS, may lead to an increased prevalence of adrenal lesions in MEN1 patients. Using EUS Schaefer et al examined the natural course and clinical relevance of small adrenal lesions in MEN1 patients. They found that during a two-years follow-up period small adrenal lesions (<3 cm) were constant in their morphology. However, further studies with large number of patients would be needed to evaluate the course of adrenal lesions in *MEN1* mutation carriers and the influence of adrenal alterations on morbidity and mortality of these patients.[37]

MEN1 Gene Mutation Screening in Patients with Adrenal Tumors: To Screen or Not?

It is well established that hyperparathyroidism occurs in almost all patients with genetically confirmed MEN1 syndrome. Using current genetic tests mutation of the *MEN1* gene can be identified in 75-77% of patients with clinically well defined MEN1 syndrome. Patients with the MEN1 phenotype in whom genetic tests fail to confirm the presence of *MEN1* gene mutation may have alterations the promoter or introns which are missed by current routine mutation screening methods.[31,36]

The predictive value of different manifestations of the MEN1 syndrome for positive *MEN1* gene mutation detection is of particular interest. It has been shown that the best predictors of a positive genetic test are the number of main MEN1-associated tumors and the family history. *MEN1* gene mutation screening in our patients with a MEN1-related state who had a high prevalence of adrenal tumors but only one of the three main components without family history of MEN1 indicated a low prevalence of *MEN1* gene mutations. This finding may suggest, that the presence of adrenal tumors has a low predictive value for a positive *MEN1* mutation screening.[36] The impact of other tumors, such as lipomas, foregut, thymic and bronchial carcinoids, ependymomas and various cutaneous lesions on the probability of a positive *MEN1* gene mutation screening has been also analysed. One prospective study conducted by Asgharian et al assessed the frequency and sensitivity/specificity of various cutaneous alterations for MEN1 in 110 consecutive patients with gastrinomas with or without MEN1 syndrome. Interestingly, the presence of more than 3 angiofibromas or any collagenoma had the highest sensitivity (75%) and specificity (95%) for a positive *MEN1* gene mutation testing. They concluded that this diagnostic criterion has a greater sensitivity for MEN1 than pituitary or adrenal disease and has a sensitivity comparable to hyperparathyroidism reported in some studies of patients with MEN1 with gastrinoma.[46]

Another possibility would be to asses the decrease of *MEN1* function in patients by direct analysis of menin expression using real-time PCR or Western blotting techniques to compare menin expression in sporadic and MEN1-associated adrenal tumors. Until recently, only a few studies assessed the menin expression in adrenal tumors. Shulte et al analyzed 14 patients with sporadic adrenal cancer and menin mRNA expression was found in all tumors. Additionally, heterozygosity for the R176Q (in one patient) and for the D418D (in 40% of patients) were identified. In another study,[21] Bhuiyan et al, analyzed 12 different sporadic adrenal tumor tissues using RT-PCR and Western blotting. Upregulation of menin in Cushing's syndrome and a decreased expression in aldosterone-producing adrenal adenoma were detected. The authors concluded that upregulation of menin expression in Cushing's syndrome may result in an altered cellular function and it may represent an early step in adrenal carcinogenesis.[47] However, no further evidence for or against this hypothesis was presented. Retention of heterozygosity of the MEN1 locus observed in adrenal

tumors of patients with MEN1 syndrome also supports the hypothesis that loss of the *MEN1* gene function is not the major cause of MEN1-associated adrenal tumors.[20,21,26]

Comments and Conclusion

Nonfunctional enlargement of one or both adrenal glands is a common finding in patients with MEN1 syndrome. In the majority of cases these adrenal lesions are hormonally inactive benign adrenocortical adenomas, but rarely pheochromocytomas, aldosterone-producing and cortisol-producing tumors and even adrenocortical carcinomas can also be found. Adrenal tumors in patients with mutations of the *MEN1* gene are phenotypically undistinguishable from their sporadic counterparts. A high prevalence of adrenal tumors in MEN-1 patients with pancreatic neuroendocrine tumors has been considered as the consequence of overexpression of growth factors such as proinsulin or insulin which may play a role in the pathomechanism of these tumors. The absence of loss of heterozygosity of the *MEN1* gene MEN1-associated adrenal tumors may indicate that inactivation of the *MEN1* gene does not rule tumorigenesis in the adrenal gland.

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