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Association of Adrenocortical Carcinoma with Familial Cancer Susceptibility Syndromes

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Abstract

Our knowledge about inherited susceptibility to adrenocortical carcinoma (ACC) almost exclusively stems from experiences with familial cancer susceptibility syndromes, which are caused by single gene mutations (e.g. Li-Fraumeni syndrome (LFS)). Population-based studies are largely unavailable. ACC diagnosed during childhood is known to be commonly part of hereditary cancer syndromes. Childhood ACC is part of the classical tumor spectrum of LFS and Beckwith-Wiedemann syndrome (BWS). In adults ACC has been reported in patients with multiple endocrine neoplasia (MEN1), familial adenomatous polyposis coli (FAP) and neurofibromatosis type 1 (NF1). However, the evidence associating ACC with these syndromes is less well substantiated. Here, we will review the evidence for genetic predisposition in general and the association with known familial cancer susceptibility syndromes in particular. We will also review current recommendations regarding screening and surveillance of these patients as they apply to a specialized ACC or endocrine cancer clinic.

1. Hereditary Aspects of Adrenocortical Carcinoma

It is well established that the risk of developing cancer is in part caused by genetic predisposition. In cases of classical familial cancer susceptibility syndromes, single gene mutations confer tumor susceptibility. However, genetic predisposition not only includes disorders caused by single gene mutations, but even more commonly occurs as a complex trait, involving multiple genes and molecular pathways. Certain alleles can be linked to promotion of tumor growth either in an intrinsic fashion or through interaction of their gene products with environmental factors.

1.1. Population-based studies

One method to estimate the genetic contribution to cancer development is through large population-based studies, such as state- or nation-wide family registries with information on cancer history in family pedigrees (Goldgar 2002; Kerber et al. 2005). The advantage of this method is that it takes into account any genetic contribution: complex traits, which involve multiple genes, as well as single gene disorders, and high penetrance alleles as well as low penetrance alleles. Two large population-based studies, the Utah population database and the Swedish Family Cancer registry, have evaluated the inherited predisposition to cancer development. Unfortunately, neither of these studies reports ACC as a separate entity, but summarizes all non-thyroid endocrine cancers in one category. The Utah study estimated the

familial relative risk (FRR) (=relative risk in 1st degree relatives) for non-thyroid endocrine cancers at 3.7 (0.3–45, 95% confidence interval) and the population attributable risk (PAR) (=the percentage of all cancers that can be attributed to a genetic predisposition) at 11% (0–20%, 95% confidence interval) depending on age with the highest value (19%) for 65–85 yrs age group (Kerber et al. 2005). The Swedish registry found a standardized incidence ratio (SIR) (=observed cases/expected cases) for non-thyroid endocrine cancers of 2.46 (1.81–3.26, 95% confidence interval) for family members with one affected parent, of 6.34 (4.44–8.79, 95% confidence interval) for one affected sibling and of 70.28 (30.01–139.15, 95% confidence interval) for one affected sibling and one affected parent (Dong et al. 2001). While this approach works well for common cancers, such as breast or colon cancer, results need to be cautiously interpreted for rare cancers. Endocrine tumors, in particular ACCs, are rare and therefore results are less reliable. This is mainly due to the fact that general epidemiological characteristics such as incidence or prevalence numbers are not well established for ACC. Furthermore, both studies presumably grouped ACC with other endocrine cancers, such as neuroendocrine tumors and pheochromocytoma/paraganglioma, which are well known to occur as part of hereditary conditions. To date, there are no population-based data in the literature that specifically focus on inherited susceptibility to ACC. Another significant limitation of population-based studies is that they rely on the premise that a syndrome is actually inherited and not due to a de novo mutation. Indeed, it is estimated that a significant amount of *TP53* mutation-caused childhood ACCs are due to de novo germline *TP53* mutations (Gonzalez et al. 2009). These would naturally completely escape any population-based study.

1.2. Family and Individual Patient Studies of Genetic Predisposition to Adrenocortical Carcinoma

In the absence of population-based studies, most of our knowledge is derived from analyses of pedigrees of families, in which family members have been diagnosed with ACC as part of a familial cancer susceptibility syndrome. Syndrome-associated gene mutations are generally inherited in a dominant fashion, resulting in a 50% chance for offspring to inherit the cancer susceptibility mutation (Nagy et al. 2004). Most of these genes are classical tumor suppressor genes. Patients are born with one germline mutated allele. The additional somatic loss of the wild type allele leads to cancer development. Analysis of affected families mainly identifies dominant alleles with relative high penetrance, neglecting the contribution of other low risk and low penetrance alleles. This bias can be regarded as a disadvantage from a research perspective, which aims to identify all genetic contributions. Clinically, it is important to be familiar with these defined familial cancer susceptibility syndromes in order to identify patients that may benefit from targeted gene testing. This may change in the future once individual genome wide sequence analysis and interpretation become available. In general, it is estimated that ~10% of all cancers are caused by single germline mutations conferring increased cancer susceptibility (Nagy et al. 2004).

The first evidence for inherited, inborn conditions predisposing to ACC was presented in a seminal analysis of a series of cases of pediatric ACC patients by Fraumeni et al. in 1967 (Fraumeni et al. 1967). The authors described a nationwide retrospective analysis of 46 children with ACC and identified several coexisting congenital conditions such as hemihypertrophy, brain and urinary tract anomalies and cutaneous lesions (e.g. café au lait spots). Of note, two children also developed astrocytomas and one child was diagnosed with an osteogenic sarcoma following radiation therapy for ACC. Interestingly, two of the described children were siblings. The association of adrenal tumors with hemihypertrophy had already been reported and was later identified as being part of the spectrum of Beckwith-Wiedemann syndrome (BWS)-related syndromes (Beckwith 1963; Riedel 1952; Wiedemann 1983; Wiedemann 1964). Further work established ACC as a core cancer of the

SBLA (sarcoma, brain cancer, breast cancer, leukemia, lung cancer, adrenocortical cancer)-syndrome, which later became known as the Li-Fraumeni syndrome (LFS) (Li et al. 1988). Although an increased risk for ACC is well established in LFS and BWS, the phenotype of developing ACC is overall of low penetrance. In both syndromes ACC occurs at a relatively young age, usually during childhood. Unfortunately, the association of ACC in adult patients with familial cancer syndromes is less well defined and will be discussed below in sections dedicated to the different syndromes.

1.3. Clinical Findings Associated with Inherited Susceptibility to Adrenocortical Carcinoma

There are several characteristics that clinically raise suspicion of a hereditary syndrome as a predisposition to cancer development (Lindor et al. 2008). In particular these are: ACC diagnosed during childhood, diagnosis of coexisting congenital malformations in an ACC patient, occurrence of bilateral or metachronous ACC, other family members affected with ACC or rare cancers, higher than usual number of affected individuals with cancer in the patient's family pedigree or second cancers in the same individual (see TABLE 1). To identify patients who are at risk of harboring a predisposing genetic mutation, it is important to obtain a detailed personal and family history. Unfortunately, family history is often inaccurate or not well documented, making retrospective analysis very difficult (Church et al. 2000; Lindor et al. 2008). In our practice it has become extremely helpful to facilitate patient evaluation by employing professional genetic counselors. To identify patients with a possible familial cancer susceptibility syndrome or other congenital syndrome, it is also necessary to obtain a thorough review of systems and perform a full physical exam with special attention to organ systems known to be related to hereditary conditions, such as the skin (e.g. café au lait spots, skin-associated tumors) or skeleton (e.g. osteomas).

Several studies provide evidence for a predisposing genetic basis in a subset of ACC patients through the evaluation of the classical indicators for inherited cancer susceptibility discussed above. As already mentioned, childhood ACC has well been described as part of hereditary cancer syndromes (Fraumeni et al. 1967; Rodriguez-Galindo et al. 2005). It is estimated that germline *TP53* mutations can be detected in 80% of children with ACC (Rodriguez-Galindo et al. 2005). The occurrence of ACC in multiple family members has also been well recognized, especially in LFS families. Bilateral or multiple primary ACCs occur in roughly 1% of ACC patients and have been described in the setting of hereditary syndromes (Bilimoria et al. 2008; Griniatsos et al. 2011; Lima Lde et al. 2011). Other primary cancers were observed in 44 of 423 patients (10.4%) in the German registry, including four patients with two other primary malignancies; in the study of Nader et al. 6 of 77 (9.1%) patients had at least one other primary malignancy and one patient had two other primary tumors (Fassnacht et al. 2010; Nader et al. 1983). However, overall data regarding family history or medical history in ACC patients is sparse and the current literature lacks detailed analyses.

2. Genetic Syndromes Associated with Adrenocortical Carcinoma

2.1. Overview of Familial Cancer Susceptibility Syndromes Associated with Adrenocortical Carcinoma

As mentioned above, the majority of childhood ACC occurs in patients with germline *TP53* mutations (~80%), but only 6.5–9.9% of all LFS patients will be diagnosed with ACC (Gonzalez et al. 2009; Olivier et al. 2003; Rodriguez- Galindo et al. 2005). In the United States, mutations in *TP53* in affected children are diverse. In contrast, a distinct mutation (*R337H*), which is found in 0.3% of the population in Southern Brazil, is found in most pediatric ACC patients in this region (Ribeiro et al. 2001). It was initially believed, that the *R337H* mutation exclusively causes pediatric ACC as a relatively low penetrance allele.

However, over recent years it has become clear that this mutation is due to a founder effect and segregates with tumor development in LFS or LFS-like families, although its penetrance is lower than that of most other LFS causing *TP53* mutations (Garritano et al.2010). It is unclear to what extent germline *TP53* mutations contribute to ACC development in the adult population. In a recent study by Gonzalez et al. in which they analyzed all patient samples sent to their institution for *TP53* gene testing, 14/21 (66%) ACC patients carried germline *TP53* mutations (Gonzalez et al. 2009). Based on this finding the authors suggest considering gene testing in all ACC patients. However, most patients with a positive test result were younger than the usual population affected by ACC (3–9.7yrs vs. 46–55yrs). Furthermore, the study may well have a referral bias, as it may be assumed that physicians sent samples for germline DNA testing based not only on the ACC diagnosis, but also on other clinical findings that suggest LFS or *TP53* mutations.

A much smaller fraction of childhood ACC arises in patients with BWS (Rodriguez-Galindo et al. 2005). This disease is caused by mutations of a genetic locus on chromosome 11p15, which harbors the *IGF2* gene, as well as several other genes (Weksberg et al. 2005). Commonly, mutations result in a relative increase in *IGF2* expression. ACCs comprise up to 20% of cancers in children with BWS, but only ~1% of children with BWS will ever develop ACC (Lapunzina 2005). ACC also occurs in idiopathic hemihypertrophy/ hemihyperplasia, which is a separate entity within the BWS-like disease spectrum and shares several features with BWS (Tan et al. 2006). In addition to tumor predisposition (e.g. Wilm's tumor, hepatoblastoma), BWS patients have variable degrees of other clinical findings, such as macrosomia, macroglossia, ear pits, omphalocele and neonatal hypoglycemia. The adrenal cortex of BWS patients is classically comprised of peculiar cytomegalic cells (Beckwith 1963; Beckwith 1998). The reason for this cytologic change is unknown, but most likely related to the effect of increased levels of *IGF2* expression and action. More common than malignant tumors of the adrenal gland are benign adrenal lesions, such as adenomas and adrenal cysts (Lapunzina 2005).

The development of BWS-associated tumors is exclusively restricted to childhood. Adult patients with a history of BWS do not seem to have an increased risk of tumor development. ACC incidence in LFS seems to decrease with age, but data on adult LFS patients are not sufficient. ACC in association with multiple endocrine neoplasia type 1 (MEN1) and familial adenomatous polyposis coli (FAP) has only been reported in adult patients. It is worthwhile mentioning, that even in syndromes, which are clearly associated with ACC (BWS, LFS), the penetrance of the ACC phenotype is very low, suggesting significant contribution of other genetic (somatic and germline) mutations.

The most common adrenocortical phenotype observed in MEN1 is unilateral or bilateral hyperplasia and (less common) adenomas (Gibril et al. 2004; Langer et al. 2002). These lesions occur in 45–55% of MEN1 patients and can be hormone secreting or non-functional. To date there have been 8 cases of ACC described in patients with MEN1 (Griniatsos et al. 2011; Haase et al.2011; Langer et al. 2002; Skogseid et al. 1992; Skogseid et al. 1995; Waldmann et al. 2007). Four of these cases had been described in the same series, estimating the risk of ACC at ~22%. In view of the overall small number of reports of ACC in MEN1, this seems to overestimate the risk. Nonetheless, it is worthwhile to consider the diagnosis of ACC, when evaluating adrenal lesions in MEN1 patients. On the same note it is worthwhile to look for MEN1 manifestations (e.g. hyperparathyroidism, neuroendocrine tumors, MEN1-specific skin findings) in ACC patients. In several cases of MEN1, accelerated growth of prior known adrenal lesions and subsequent diagnosis of ACC has been described. This suggests that ACC may arise from precursor lesions in the setting of MEN1.

There have been 6 cases of ACC described in FAP patients (Gaujoux et al. 2011; Marshall et al. 1967; Painter et al. 1985; Seki et al. 1992; Traill et al. 1995; Wakatsuki et al. 1998). As this association has commonly been mentioned in literature reviews, it is likely that not all cases are reported anymore. Interestingly, one of the ACCs had a somewhat atypical histology (sex cord-like appearance) (Wakatsuki et al. 1998). Overall adrenal adenomas, whether functional or non-functional, are much more common than ACC in FAP patients (7.4–13%), and more common in FAP than in the general population (~5%) (Marchesa et al. 1997; Smith et al. 2000). A causative relationship of ACC development and FAP is supported by the well characterized activating mutations of WNT/beta-catenin pathway components in a high percentage of sporadic adrenal tumors (Tissier et al. 2005).

In addition to the above mentioned syndromes, ACC has been reported in 4 patients with neurofibromatosis type 1 (NF1), of which at least 2 were children diagnosed at a very early age (Fienman et al. 1970; Sorensen et al. 1986; Wagner et al. 2005). No gene testing has been reported in these patients, raising the possibility of another syndrome, phenocopying NF1, such as homozygozity for gene mutations causing hereditary non-polyposis colon cancer (HNPCC). Interestingly, ACC has also been described as an atypical tumor in at least 4 cases of HNPCC (Berends et al. 2000; Broaddus et al. 2004; Medina-Arana et al.). Lastly, there are also reports of ACC in patients with Werner syndrome (Takazawa et al. 2004). However, ACC is not a typical tumor found in this patient population.

2.2. Screening Recommendations and Patient Surveillance

Careful evaluation of the patient for familial cancer susceptibility syndromes offers two major advantages, stratification of patient surveillance and possible identification of family members at risk for ACC or other tumor development. It is equally important to identify family members not at risk, who may be spared of unnecessary screening procedures. The only general genetic screening recommendation that can be deduced from the current literature is testing for alterations of the *TP53* gene (Gonzalez et al. 2009; Tinat et al. 2009). Although the main basis for this recommendation is a retrospective study of patients referred for genetic testing and may, therefore, harbor a significant referral bias (see above). Testing should be encouraged until more evidence accumulates regarding germline *TP53* mutations in the adult ACC population. Testing for any other syndrome should be guided by patient history, family history and physical exam findings. Cost-effectiveness of genetic screening is controversial for common malignancies associated with relatively common hereditary tumor predisposition (e.g. HNPCC), but no data is available for ACC (Dinh et al. 2011). In our experience, every patient undergoing genetic testing should be referred for consultation with a clinical geneticist. The expertise of a clinical geneticist will guide genetic testing (e.g. prioritization of genes to test), identify family members best suited for initial testing, and interpret results with respect to their contribution to tumor development (e.g. allele segregation amongst affected family members). In addition, genetic counselors will address medical questions regarding genetic testing and psycho-social issues, such as test-related stress, coordination of family testing and legal issues.

The rationale for tailored screening procedures aimed at tumor detection in patients at risk is based on the premise that early detection of a cancer may increase chances for cure. While to date this has not been shown for patients at risk for ACC, it seems logical as patient survival is better at earlier stages of the disease. Only early stages of ACC are amendable for a curative, surgical approach. While cost-effectiveness of cancer screening is not considered controversial in more common familial cancer susceptibility syndromes with well defined cancers, such as colon cancer in HNPCC, for which well established screening procedures are available (colonoscopy), no data are available for ACC.

Certainly, for a rare cancer, such as ACC, there is no screening recommendation for the general population and even in patients at risk there is no established biochemical or imaging screening tool that has a grade of sensitivity to be useful in this setting. Currently, imaging procedures are most likely of the greatest value. However, even this approach is hampered by the relatively high incidence of benign adrenal lesions and, in case of the presence of other malignancies, adrenal metastasis. In addition, screening may rely on patient history, review of systems and physical exam, which may uncover excess hormone production or abdominal tumors.

Surveillance recommendations for LFS, BWS, FAP, MEN1 and NF1 affected patients do not specifically include any screening for ACC (Brandi et al. 2001; Clericuzio et al. 2009; Ferner et al. 2007; NCCN 2011; Tan et al. 2006; Vasen et al. 2008). Nonetheless, some of the recommended screening procedures may identify ACC. In general, screening in LFS is difficult due to the many different cancers associated with this syndrome. While there had not been extensive studies addressing the question of screening for cancers in LFS patients, a very recent study showed that a screening program is feasible and that screening related early detection of tumors may translate into decreased mortality amongst *TP53* mutation carriers. Of note, amongst the detected tumors were 2 ACCs, which were found by a screening protocol using ultrasound imaging and endocrine evaluation (testosterone, DHEAS, androstenedione, 17-OH-progesterone) in four month intervals (Villani et al. 2011). The current NCCN guidelines for LFS recommend yearly comprehensive physical exams starting at the time of diagnosis. The physical exam should be conducted with a high suspicion for rare cancers. In accordance with this recommendation children with known germline *TP53* mutation should be followed for abnormal sexual development, precocious puberty as a possible manifestation of excess sex steroid secretion, or symptoms and signs of Cushing syndrome. It is important to consider minimizing radiation exposure with screening procedures, because radiation may induce cancers in this population. Several ongoing studies utilize whole body MRI and ultrasound techniques for screening to detect cancers while minimizing radiation exposure. For BWS regular screening for Wilms tumor and hepatoblastoma is recommended until an age after which tumor risk considerably decreases. These imaging procedures may very well also visualize the area of the adrenal gland. The guidelines for FAP mention adrenocortical tumors, but do not suggest specific screening. Biennial CT scans of the pancreas are recommended for MEN1 patients, which will also visualize the adrenal glands. Special attention in this population should be paid to enlargement of preexisting adrenal lesions (see above). NF1 patients undergo yearly exams with a special focus on pubertal development, but no imaging procedures. Due to the increased risk of pheochromocytoma and renal artery stenosis, regular blood pressure measurements are recommended. Both screening procedures can potentially detect at least some of the hormone-secreting adrenal lesions.

In summary, ACC has been well documented in some familial cancer susceptibility syndromes, while to date the evidence for an association with others is less sufficient. Hopefully, future whole genome analyses together with population and registry based studies will solidify evidence for the association of ACC with these syndromes and uncover new associations. Whole genome analyses as conducted for several cancers will add significant knowledge about predisposition to ACC development. Clinically it is important to consider the occurrence of ACC as part of a syndrome as it may guide therapy (e.g. caution with radiation therapy in LFS patients), give the possibility for individualized screening for other commonly observed cancers in these syndromes, and identify family members at risk.

3. Comment

This article presents a summary of an oral presentation at the 3rd Adrenal Cancer Symposium in Wuerzburg, Germany.

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Table 1

Summary of features in past medical history and family history suggesting the presence of hereditary cancer susceptibility syndromes in adrenocortical carcinoma (ACC) patients.

Features suggesting the presence of a hereditary cancer susceptibility syndrome in ACC patients
Personal history
Metachronous ACC
Bilateral ACC
Multiple primary tumors in organs other than the adrenal gland
Other rare cancers in the same patient
Development of ACC from prior known precursor lesion
ACC diagnosed during childhood
Other congenital defects
Other endocrine diseases (e.g. pHPT)
Cutaneous lesions commonly found in hereditary cancer susceptibility syndromes
Family History
Unusual high number of family members affected with cancers
Family history of ACC
Family history of other rare cancers
Family history of known hereditary cancer susceptibility syndromes