Syndromes associated with abnormalities in the adrenal cortex

Chien Chen
Jennifer L Hunt

Abstract

Recognizing that adrenal pathology is a component of many genetic syndromes is important for clinical management and genetic counselling. These syndromes may be divided into those which cause excessive adrenal growth including tumours, and those which cause hypoplasia or destruction of the adrenal glands. Syndromes associated with hyperplasia and tumour development include Beckwith-Wiedemann, Li-Fraumeni, Carney complex, McCune-Albright, multiple endocrine neoplasia type 1, hereditary nonpolyposis colorectal carcinoma, familial adenomatous polyposis, primary bilateral macronodular adrenal hyperplasia, and congenital adrenal hyperplasia. Syndromes associated with adrenal dysgenesis or atrophy include X-linked adrenal hypoplasia, IMAGe syndrome, MIRAGE syndrome, familial glucocorticoid deficiency, X-linked adrenoleucodystrophy, Allgrove syndrome, Wolman syndrome, autoimmune polyendocrine syndrome and steroid resistant nephrotic syndrome. The clinical, genetic, and histopathological features of each disease will be discussed.

Keywords adrenal cortex; Beckwith-Weidemann; congenital adrenal hyperplasia; congenital adrenal hypoplasia; Li-Fraumeni; McCune-Albright; MEN-1; syndrome; X-linked adrenoleucodystrophy

Introduction

The adrenal gland is an endocrine organ essential for many functions of the human body. A number of syndromes and hereditary conditions are associated with abnormalities in the adrenal cortex. This review will focus on the syndromes and genetic conditions that affect the adrenal cortex and their associated histopathological findings (Table 1). The clinical manifestations, molecular basis and histopathology for each entity will be discussed. The syndromes are divided into those that cause adrenal cortical overgrowth, including tumours, and those that are cause adrenal dysgenesis or atrophy.

Syndromes associated with adrenal tumours and nodular hyperplasia

Beckwith-Wiedemann syndrome (Table 2)

Beckwith-Wiedemann syndrome (BWS) is a rare (1:13,700)[1] overgrowth syndrome first described by Beckwith (1963)[2]; and Wiedemann (1964).[3] Roughly 85% of BWS cases are sporadic, with the remainder inherited in an autosomal dominant, maternal inheritance manner. Prenatal abnormalities include polyhydramnios, large placenta, sometimes with placental mesenchymal dysplasia, and excessive umbilical cord length.[1] Patients with BWS may present with a constellation of physical features, most commonly, macroglossia, macrosomia, abdominal wall defects or malrotation (omphalocoele, diastasis recti and umbilical hernias), and visceromegaly (hepatomegaly, nephromegaly, pancreatomegaly).[4,5] Additional findings include neonatal hypoglycaemia, hemihyperplasia, nevus flammeus, ear lobe pits or posterior helical pits, renal dysplasia, cardiac anomalies (cardiomegaly, structural abnormalities, cardiomyopathy), midface hypoplasia and advanced bone age.[4] BWS is associated with an increased risk of malignancy (overall 5−10%), the most common of which is Wilms tumour, but include hepatoblastoma, rhabdomyosarcoma, neuroblastoma and adrenal cortical carcinoma (ACC).[1] Clinical presentation and tumour risk is variable and dependent on the molecular genotype.[5–7]

BWS is the result of overexpression of *IGF2* and/or silencing of *CDKN1C* but its genetics is complicated by genetic imprinting (the differential expression of genes based on the parent of origin, usually as a result of differential DNA methylation).[5] Two clusters of imprinted genes within 11p15 designated the IGF2/H19 and CDKN1C/KCNQ1OT1 domains are responsible for BWS. The IGF2/H19 domain contains the *IGF2* and *H19* genes and is controlled by the imprinting control region H19DMR. Methylation of H19DMR, the maternal pattern, results in expression of H19 and suppression of IGF2 while demethylation, the paternal pattern, reverses the expression profile. The CDKN1C/KCNQ1OT1 domain contains multiple imprinted genes, the most important of which are *CDNK1C* and *KCNQ1OT1*, under the control of the KvDMR1 imprinting control region. *KCNQ10T1* produces a long RNA transcript which appears to coat the CDKN1C/KCNQ1OT1 domain, suppressing *CDNK1C* and the other genes in the region. Methylation of KvDMR1, the maternal pattern, suppresses KCNQ10T1 and activates *CDNK1C* as well as other genes in the region.[7]

The vast majority of sporadic BWS cases are associated with imprinting abnormalities in the 11p15 region.[5–7] Roughly half show loss of methylation of the maternal KvDMR1, another 2−7% show gain of methylation of the paternal H19DMR and 20% show paternal uniparental disomy of the 11pq15 region. These imprinting abnormalities are mosaic in patients, further complicating the phenotype.[5,7] The impact of this mosaicism is highlighted by studies of monozygotic twins in BWS, who frequently show discordant phenotypes.[8] Less than 7% of sporadic BWS patients have DNA sequence aberrations, the most common of which are loss of function mutations of CDKN1C (~5%) along with translocations, inversions or duplications (1−2%). Unlike imprinting abnormalities, these sequence aberrations are not mosaic and are the most common cause of familial BWS.[7] While the overall risk of malignancy is 5−10%, it varies based on the genetic abnormality, with the lowest risk associated with loss of methylation at the maternal KvDMR1 (risk <3%), and the highest risk with gain of methylation at the paternal H19DMR (>25%).[6,7]

Chien Chen *MD PhD is an Assistant Professor at the University of Arkansas for Medical Sciences, Little Rock, AR, USA. Conflicts of interest: none declared.*

Jennifer L Hunt *MD Med is the Chairman of the Department of Pathology at the University of Arkansas for Medical Sciences, Little Rock, AR, USA. Conflicts of interest: none declared.*

Overview of pathologic finding in syndromes involving the adrenal cortex

Adrenocortical Pathology	Associated Syndromes
Bilateral macronodular adrenal hyperplasia	Primary bilateral macronodular adrenal hyperplasia Congenital adrenal hyperplasia Multiple endocrine neoplasia type 1 Familial adenomatous polyposis McCune Albright syndrome Beckwith Weidemann Syndrome
Primary pigmented nodular adrenal disease	Familial primary pigmented nodular adrenal disease Carney Complex
Adrenocortical adenoma	Multiple endocrine neoplasia type 1 McCune Albright syndrome Carney Complex Familial adenomatous polyposis Beckwith Weidemann syndrome Congenital adrenal hyperplasia
Adrenocortical carcinoma	Li-Fraumeni syndrome Beckwith Weidemann Syndrome Multiple endocrine neoplasia type 1 Familial adenomatous polyposis Hereditary nonpolyposis colorectal carcinoma
Adrenocortical hypoplasia	X-linked adrenal hypoplasia IMAGe syndrome MIRAGE syndrome Familial glucocorticoid deficiency (some forms)
Adrenocortical atrophy	Autoimmune polyglandular syndrome Allgrove syndrome X-linked adrenoleukodystrophy Familial glucocorticoid deficiency (some forms) Steroid resistant nephrotic syndrome
Adrenocortical calcifications	Wolman syndrome

Table 1

Adrenocortical pathology in BWS may include adrenocortical cysts, cortical hyperplasia, and sometimes, marked adrenocortical cytomegaly.[2,9,10] The cytomegaly often lines the cysts or pseudocysts of the adrenal cortex. Adrenal cortical tumours have also been described, including both adrenal cortical adenomas (ACA) and ACC.[9,10] Like other malignancies associated with BWS, the increased risk for ACC appears to be largely restricted to early childhood.[9]

Li-Fraumeni syndrome (Table 3)

Li-Fraumeni syndrome (LFS) is an autosomal dominant cancer predisposition syndrome characterized by a very high lifetime risk for cancer and an early age of initial cancer diagnosis.[11,12] The most common malignancies (Figure 1) associated with LFS include bone and soft tissue sarcomas, breast carcinomas, brain tumours, ACCs and leukaemias. Other less common tumours include gastric carcinoma, colorectal carcinoma, pancreatic carcinoma and Wilms tumour.[11–13] ACCs are reported in approximately 6–13% of patients with LFS,[12] usually in childhood but also in adults.[9,10] In fact, 50–80% of children presenting with ACC have LFS.[9,10]

The genetic basis for LFS is a germline mutation in the *TP53* tumour suppressor gene. *TP53* encodes p53, a homo-tetramer DNA binding protein involved in cell cycle arrest, DNA repair, apoptosis, senescence, and differentiation.[14] Germline mutations in *TP53* are generally point mutations, generally missense and can occur anywhere in the 11 exons of the gene, but most occur in exons 5–8 which encode the DNA binding domain of p53[13,14] (Figure 2). Carcinogenesis is believed to occur through three mechanisms: dominant negative effects on DNA binding by hetero-tetramers of wildtype and mutant p53, loss of heterozygosity (LOH) through mutation of the wildtype TP53 allele, and poorly understood gain of function mutations.[14]

The most common adrenal cortical lesion in LFS is ACC,[10] which is histologically indistinguishable from sporadic forms of the tumour. Differentiating between benign and malignant cortical lesions remains challenging, and relies on a constellation of clinicopathological features. Large tumours and those with haemorrhage, necrosis and capsular invasion are much more suspicious for malignancy. Other malignant features include marked nuclear atypia, atypical or frequent mitotic figures (>5 per 50 high powered fields), and vascular invasion.[15]

Carney complex (Table 4)

Carney complex (CNC) is a very rare (~750 cases in the largest registries)[16] autosomal dominant multiple endocrine neoplasia and cardiocutaneous syndrome, first described by Carney in 1985 as a combination of myxomas, spotty pigmentation and endocrine overactivity.[17] Roughly 70% of CNC cases are inherited and the remaining 30% arise from de novo germline mutations.[16] While it has a very high penetrance, its phenotype is quite variable and progressive, with a median age of diagnosis around 20 years of age.[16,18]

Patients with CNC have a variety of clinical findings. These include a characteristic distribution of lentigenes (lips, conjunctiva, inner and outer canthi, and the vaginal/penile mucosa), café au lait spots, and epitheliod blue nevi, a very rare finding in the general population.[16,18] Myxomas are common and may be found in the skin, mucosa, heart and sometimes breast.[18] Multiple endocrine abnormalities are seen, including pituitary somatotroph hyperplasia, growth hormone secreting pituitary adenomas, thyroid adenomas and carcinomas and adrenal abnormalities.[16,18] Psammomatous melanocytic schwannomas, large-cell calcifying Sertoli cell tumours of the testes, and breast ductal adenoma and myxoid fibroadenomas are other conditions that are associated with CNC.[16] Although rare (~1% of CNC patients), osteochrondomyxomas of the bone are strongly associated with CNC.[16,18]

Linkage analysis has localized CNC to two loci, CNC1 (17q22–24) and CNC2 (2p16).[16,18] While the genes involved in CNC2 remain unidentified, those patients whose disease maps to CNC1 consistently show inactivating mutations in *PRKAR1A*, which accounts for ~70% of all CNC cases.[16] Most mutations are unique