Chapter 13
Cowden Disease, Lhermitte-Duclos Disease, and Bannayan-Riley-Ruvalcaba Syndrome

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Contents

Introduction

CS is a sporadic genodermatosis of autosomal dominant inheritance and incomplete penetrance. As of today, less than 250 cases have been reported in the literature. *PTEN* hamartoma tumor syndrome refers to a spectrum of disorders linked to autosomal dominant mutations in the *PTEN* gene with loss of heterozygosity at 10q23, namely, *Cowden* disease (CD), *Bannayan-Riley-Ruvalcaba* syndrome (BRRS), adult *Lhermitte-Duclos* disease (LDD), and autism spectrum disorders associated with macrocephaly. The protein coded by *PTEN* comprises 403 amino acids and acts as a negative regulator of the PI3K/Akt signaling pathway by dephosphorylating PIP3 *(phosphatidylinositol-3 kinase).* The protein is almost ubiquitously expressed in the body. In the bibliography, the majority of published data affect cases with *Cowden* syndrome. To the present, there is a lack of correlation between specific *PTEN* mutations and clinical presentation [1, 2].

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Lloyd and Dennis reported the first description of Cowden's disease in 1963 [3]. Diagnostic criteria were initially proposed by *Salem* and *Steck* in 1983 [4] and revised further by consensus of an international consortium of researchers in 1996 before the identification of the gene [5]. *Cowden's* disease is rare, characterized by facial papules (trichilemmomas), gingival papillomas (frequently), keratoses of the palms and soles, and an increased risk for malignancies in the breast and thyroid.

Lhermitte-Duclos disease, first described in 1920 [6], presents with abnormal development and unilateral hemispheric expansion of the cerebellum. It is often associated with Cowden disease [1, 2, 7, 8].

Clinical Characteristics

Although the published data are limited, the estimated prevalence of CS is 1/200,000 individuals. *Cowden* disease shows cutaneous manifestations, such as mucocutaneous facial papules, gingival papillomas, and keratoses of the palms and soles. Mucocutaneous lesions are present in about 100% of affected individuals. Systemic hamartomas are common, and there is high risk of breast, thyroid, genitourinary, polydactyly, and endometrial malignancies, as well as benign hamartomatous overgrowth of tissues (skin, colon, thyroid). Benign thyroid disease is expected in 50–70% of the patients [7, 9, 10].

Lhermitte-Duclos disease, or dysplastic cerebellar gangliocytoma, is a peculiar hamartoma arising from the cerebellar cortex, often associated with cerebellar dysfunction, with diffuse hypertrophy of the stratum granulosum likely to be caused by mutations of the *PTEN* gene [7, 11, 12] (see Chap. 4). The clinical presentation is typically characterized by cerebellar dysfunction, ataxia, headaches, visual disturbances, gait disturbances, occlusive hydrocephalus, and cranial nerve dysfunction in young adults, although the age of onset ranges from birth to sixth decade [1, 12]. According to *Vinchon* et al. [13] one-third of the approximately 80 reported patients died as a direct result of mass effect from the cerebellar gangliocytoma. So far, 221 cases of this disease have been reported in the medical literature.

An association between *Lhermitte-Duclos* and *Cowden* disease was first recognized by *Padberg* et al. [14] and *Albrecht* et al. [15]. The *Cowden-Lhermitte-Duclos* complex represents a true *"neurocutaneous syndrome."* More than 70 mutations have been described in the *PTEN* gene in patients with *Cowden* syndrome [10]. The coexistence of these two rare disorders is often underrecognized and underreported.

Bannayan-Riley-Ruvalcaba syndrome is an autosomal dominant genetic disease, characterized by diverse clinical manifestations of excessive growth before and after birth (large birth weight). *Clinical characteristics* include macrocephaly, lipomas, retinal malformations, benign hamartomas of the subcutaneous tissue, within the intestines or of the pharynx and tonsils, and/or abnormally pigmented areas of skin. Macrocephaly is found in the majority of BRRS patients. Other symptoms

include developmental delay, vascular anomalies, seldom hemimegalencephaly and uveitis, and joint hyperextensibility [7, 16–18].

Macrocephaly (defined as a head circumference greater than the 97th percentile) has been found in 80–100% of patients with *PTEN* mutations. Further diagnostic workup is necessary if skull circumference increases extremely and symptoms of intracranial pressure develop [18, 19].

Diagnosis

The diagnosis is established clinically by the presence of mucocutaneous lesions, for example, six or more papules, at least three of which are trichilemmomas, which are wart-like adnexal tumors that arise near hair follicles, cutaneous facial papules, palmoplantar keratoses, and cobblestoning of the oral mucosa, or by a combination of one major criterion, e.g., breast cancer, endometrial carcinoma, thyroid cancer, macrocephaly, or macular pigmentation of the glans penis (present in almost half of the male patients), and one minor criterion, e.g., thyroid lesions, renal cell carcinoma, mental retardation, lipomas, autism, fibromas, or vascular abnormalities [5].

The diagnostic criteria proposed by *Pilarski* et al. [9] encompass wider phenotypes associated with *PTEN* mutations in about 80% of the cases. They have been tested on only a small group of patients, and further assessment and application in the clinical practice will be required to determine their utility. According to *Tan* and *Eng* [20], the criteria are unacceptable by modern diagnostic standards. *Other* related disorders caused by mutations of the *PTEN* gene include *Proteus syndrome* as well as hereditary mixed polyposis syndrome (see Chap. 22). The diagnosis is based on clinical criteria [11, 21, 22]. In Lhermitte-Duclos, the MRI (radiological findings) is an important tool for establishing the diagnosis by demonstrating typical striated, laminar/tigroid folial pattern of the cerebellum [1, 2, 8].

Therapy

The management is symptomamatic, and patients should be looked after on a regular basis by an experienced multidisciplinary team. In addition to surgical management of existing lesions, there are several clinical trials with PI3K/AKT/mTOR pathway inhibitors on the way [23, 24]. For PHTS, direct inhibition of PI3K is the most attractive therapeutic prospect. Further, sirolimus has been used. Three treatments with this mTOR inhibitor were reported. Two patients had severe forms of PHTS. Upon treatment with sirolimus, the size of lipomatous and vascular lesions improved. However, the effects reversed when the drug was discontinued, suggesting a rather preventive action and the necessity of long-term administration [23, 24].

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