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Case report

Cowden syndrome and the associated Lhermitte-Duclos disease – Case presentation

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ABSTRACT

We report a patient with features of Cowden syndrome (CS). A 35-year old woman has been suffering from headache, vertigo and mild imbalance since 2 years. Examination showed subtle mucocutaneous lesions: papillomatous papules on the gingival mucosa, a few verrucous acral skin lesions and macrocephaly. Magnetic resonance imaging (MRI) revealed a tumor of the left cerebellar hemisphere with ''tiger-striped'' pattern on T2-weighted image (T2WI), typical of Lhermitte-Duclos disease (LDD) – one of the pathognomonic but infrequent features of CS. A pathogenic de novo heterozygous PTEN mutation: c.49C>T variant has been identified in exon 1 of the *PTEN* gene by sequencing.

1. Introduction

Cowden syndrome (CS) MIM 158350 is a rare, clinically heterogeneous disorder, inherited in an autosomal dominant manner. It is characterized by multiple hamartomatous tumors originating from all three embryonic layers and increased risk of different malignancies. About 80% of the cases result from germline mutations in the tumor suppressor gene *PTEN*, located on chromosome 10q22-23 [1]. The gene spans nine exons and encodes a phosphatase amino acid protein that regulates the cellular growth, apoptosis, migration as well as angiogenesis. The mutations in *PTEN* gene cause several PTEN hamartoma tumor syndromes (PHTSs), including Cowden, Bannayan–Riley–Ruvalcaba, Proteus syndromes and Lhermitte-Duclos disease [2]. Previous studies have described symptoms overlapping in these conditions [3,4]. Lachlan et al. even suggested that Cowden syndrome and Bannayan–Riley–Ruvalcaba syndrome are one disease with inter- and intrafamilial clinical variability and age-related penetrance [5]. Germline PTEN mutations have also been found in autism spectrum disorders with macrocephaly [6]. Somatic mutations of the *PTEN* gene were identified in various tumors, such as, in glioblastomas, melanomas, carcinomas of endometrium, breast, prostate and thyroid [7–12].

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CS was first described by Lloyd and Dennis in 1963 in a women, Rachel Cowden [13]. The prevalence of CS is estimated between 1:200 000 and 1:250 000 individuals [14,15] with predominance in Caucasians and in females [16]. There is wide clinical variability in severity of phenotypes and individuals with subtle features of the syndrome may remain unrecognized [17–19]. Trichilemmomas (hamartomas of the outer sheath epithelium of the hair follicle), papillomatous papules (benign lesions of epithelium) on the face and oral mucosa with cobblestone appearance on the buccal and gingival mucosa as well as acral and plantar keratoses are pathognomonic mucocutaneous features of CS. 99% of the patients with CS reveal these symptoms by their third decade of life [2]. The gastrointestinal lesions are present in 70–85% of the cases, including polyps and glycogenic acanthosis (white plaques in the distal esophagus consisting of glycogen-filled squamous cells) [20,21]. Patients with CS are at increased risk to develop of benign and malignant tumors of some organs, predominantly: breast, thyroid, endometrium, colon and renal cells [22–26]. Previous reports described occurrence of multiple arteriovenous malformations (AVMs) in the pelvis, liver, cervical vertebra as well as bleeding from AVMs of the small intestine [27,28]. The clinical diagnosis of CS is based on diagnostic criteria established by International Cowden Consortium [29].

Adult–onset Lhermitte-Duclos disease (LDD) associated with CS, characterized by slowly growing cerebellar hamartoma (dysplastic gangliocytoma), was recognized to be one of the CS pathognomonic criteria since 2004. The clinical picture of LDD is associated with the enlarging tumor in the posterior cranial fossa, resulting in cerebellar dysfunction and raised intracranial pressure. Sometimes the patients complain of headache and mild instability only, but vomiting, dysarthria, dysphagia, ataxia and visual disturbances may also occur [30]. Usually LDD has insidious onset and slow progression, although there are some reports of sudden onset with severe clinical presentation of LDD [31]. Almost all adult individuals with LDD had *PTEN* mutations [32].

Here we report a patient affected with Lherimitte-Duclos disease – one of the PTEN hamartoma tumor syndromes considered as phenotypic variant of CS.

2. Case presentation

A 35-year old woman was referred to our Genetic Department with suspicion of Cowden syndrome. Magnetic resonance imaging showed a lesion of the left cerebellar hemisphere, with the characteristic ''tiger-striped'' appearance on T2-weighted image (T2WI), measuring 35 mm × 20 mm × 25 mm and slightly compressing fourth ventricle (Fig. 1). Initially, this lesion has been considered as being of a vascular origin but another radiologist who consulted the patient (ADZ) suggested the diagnosis of CS. The tumor has not progressed to date (Fig. 1) and has remained without surgical intervention, but the neurosurgeons recommended MRI every 6 months.

The patient has been complaining of headache, vertigo and mild gait imbalance since 2 years. At 26 years of age, she underwent gynecological diagnostics due to paramenia and ultrasonography showed bilateral ovarian cysts. She had also nodular goiter (diagnosed by ultrasonography and fine-needle biopsy) and hypothyroidism treated to date by Euthyrox. She has had recurrent increased blood sugar levels and needed anti-diabetic drugs. Endoscopy, performed due to gastric complaints, when she was 34 years old, revealed erosive gastritis, two polyps in cardia region of stomach and multiple white plaques in distal part of esophagus, recognized as glycogenic acanthosis. She has been diagnosed and treated with gastrointestinal mycosis.

The patient is the third child of non-consanguineous parents. She has four healthy siblings and no children (Fig. 2).

There was no family history of neoplastic disorders. The patient's mother at 47 years of age had subarachnoid hemorrhage but no aneurysm or arteriovenous malformation have been found in her. She was under gynecologist care because of irregular menstruation. The father of the patient has had right side hearing impairment and received treatment because of the increased glycaemia.

3. Results

Physical examination of the patient showed several very small papillomatous papules with cobblestone appearance on the gingival mucosa, a few verrucous acral skin lesions, measuring 0.2–0.3 cm and large head circumference – 59 cm (size greater than the 97th percentile). The neurological status was normal.

The informed consent was obtained from the molecularly tested family members. Genomic DNA was extracted from peripheral blood through the standardized phenol/chloroform extraction method. The genetic study was carried out in Genetic Diagnostic Network (Gendia, Belgium, Antwerp). Sequencing of the promoter region and the entire coding region (exons 1–9) and of all intron–exon boundaries as well as and the core promoter of the *PTEN* gene was performed. A pathogenic heterozygous *PTEN* mutation: c.49C>T variant was identified in exon 1 of the *PTEN* gene by sequencing. This variant is a nonsense mutation predicted to lead to the substitution of a glutamine by a premature stop codon on position 17 (p.Gln17X), resulting in a truncated PTEN protein or diminished PTEN mRNA due to mRNA decay. This is a known change previously reported in other patients [33] and it is classified as a pathogenic variant according to the Mutation Database criteria.

The physical and neurological examination of the patient's parents did not reveal any abnormality and DNA analysis performed in them did not show the mutation found in their affected daughter – so the mutation in the proband was a new one (*de novo* mutation).

4. Discussion

The mutation in the first exon of the *PTEN* gene found in the presented case has already been identified in other patients [33] however according to the literature most of mutations in CS have been detected in exons 5, 7 and 8 [34]. In 40–60% of the reported cases the mutations of the *PTEN* gene in CS are de novo and our case belongs to this category.

Cowden syndrome is recognized using International Cowden Consortium Diagnostic Criteria [29]. The pathognomonic mucocutaneous features of CS are observed before the third

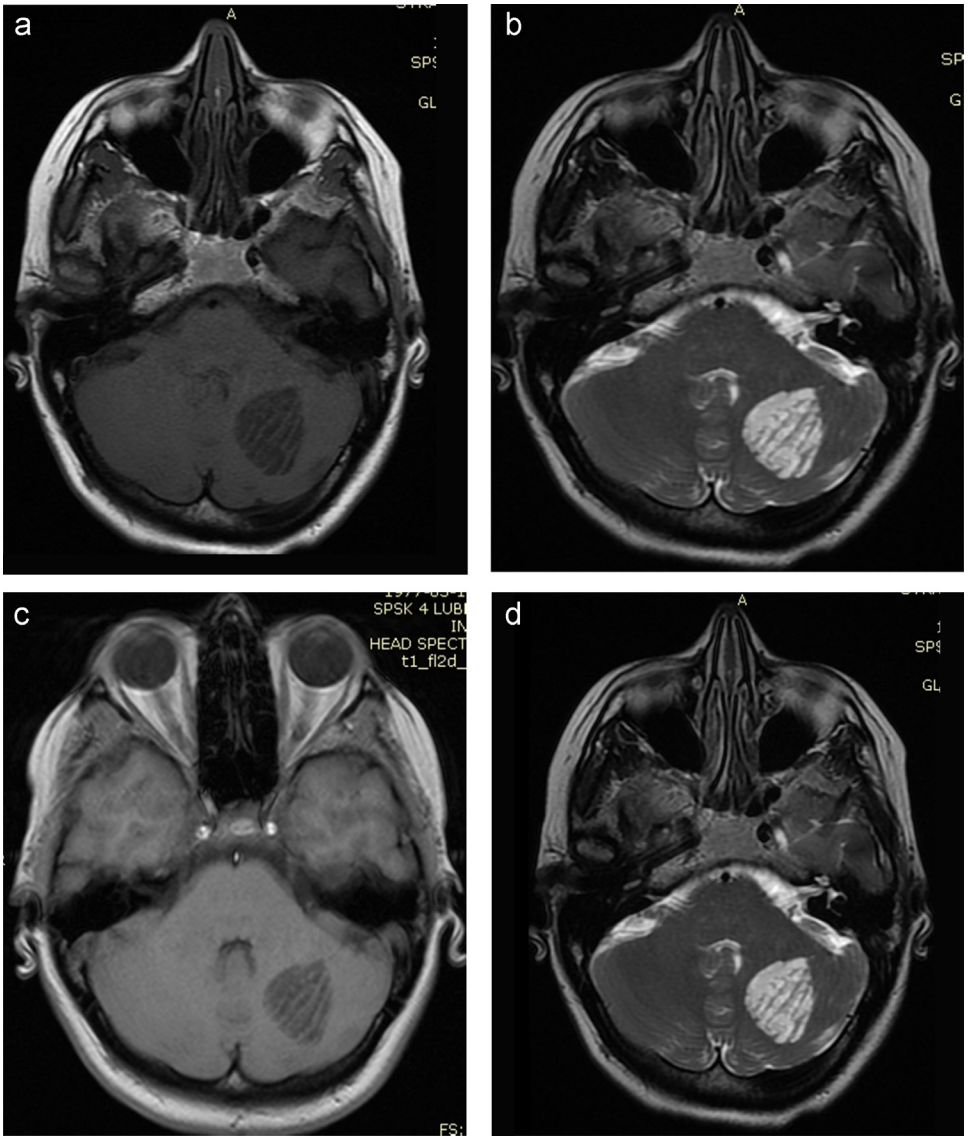

Fig. 1 – Magnetic resonance imaging of the brain performed in November 2011 (A and B) and in February 2013 (C and D) – Progression has not been observed. (A and C) T1-weighted axial images showing hypointense tumor of left cerebellar hemisphere with isointense strips. (B and D) T2-weighted axial images showing hyperintense lesion with linear hypointensity strips. Cerebellar alteration slightly compresses fourth ventricle. The "tiger-striped" MRI appearance of this lesion is characteristic of Lhermitte-Duclos disease.

decade of life [2]. They may be subtle and unnoticed by the patients and by the physicians. The adult onset LDD is a rare condition associated with and pathognomonic of CS caused by the mutations in *PTEN* gene. However it is worth to note that no

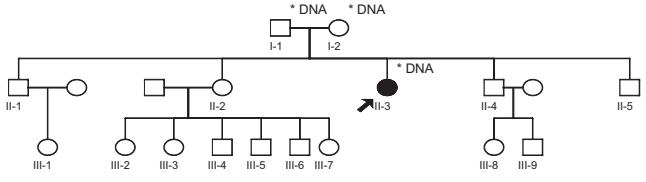

Fig. 2 – Pedigree of the family. The filled symbol indicates the affected woman (II-3) with a detected *PTEN* gene de novo mutation (no mutation in *PTEN* gene was found in her parents).

changes of *PTEN* gene have been identified in children with LDD [32]. Despite the fact that LDD progresses usually slowly, it is a life-threatening condition, resulting in increased intracranial pressure and neurological and sometimes visual disturbances. Symptomatic LDD patients should undergo the surgical resection of the tumor. The regrowth of cerebellar gangliocytoma has been observed [35], thus individuals after surgical intervention should under radiological and neurosurgical care. The LDD is a rare condition and its frequency in patients with CS is yet unknown [34]. In CS patients, variable benign alterations may be found, such as thyroid lesions (multinodular goiter, adenomas, hamartomas), fibrocystic breast disease, uterine fibroids or leiomyomas, bicornate uterus, lipomas, fibromas and vascular anomalies. Macrocephaly occurs in up to 100% of the cases [5]. Among the rarer symptoms of CS, developmental delay and

gothic palate (up to 15%) have been observed. The most dangerous for the patients, however, is predilection to malignancies, particularly of the breast, thyroid and endometrium cancer.

Authors of numerous studies described also high incidence of gastrointestinal polyps of different histological type in PTEN mutations carriers and increased risk of gastrointestinal malignancies in them [3,4,27].

Given increased susceptibility to benign and malignant tumors, the CS patients should be screened for cancer, according to the National Comprehensive Cancer Network (NCCN) guidelines [36].

The presented patient met CS criteria established by International Cowden Consortium [30]. Her left cerebellar hemisphere tumor was the first finding, which could be considered as characteristic of Lhermitte-Duclos disease associated with CS. The macrocephaly was not noticeable although the patient declared that she often had difficulty with matching caps and hats. Mucocutaneous lesions were weakly expressed: she noticed but has never reported them to the physicians. The tumor has not progressed to date (Fig. 1) and has remained without surgical intervention, but the neurosurgeons recommended MRI every 6 months. After establishing the diagnosis of CS, a series of investigations have been carried out. Ultrasonography showed multiple cysts in the breast. Thyroid and endometrial ultrasonography carried out earlier did not show any changes. The plans for near future are: breast biopsy, colonoscopy and gastroscopy. The patient will be screened according to NCCN guidelines [36].

The present case demonstrates the importance of genetic testing of the affected persons and their family members in the process of establishing or confirming the diagnosis which consequently enables clinicians to offer proper treatment, preventive measures and genetic counseling.

Conflict of interest

None declared.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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