Short Report

Hereditary trichilemmal cysts: a proposal for the assessment of diagnostic clinical criteria

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Trichilemmal cysts (TCs) can occur as sporadic lesions or in hereditary–familial settings with autosomal dominant transmission. These entities have not been widely analyzed in their peculiar aspects yet. The aim of this study was to describe a cohort of patients with diagnosis of TCs through a clinical and biomolecular characterization, intended to highlight some effective diagnostic criteria for their identification. Among 149 cases of this study, 24 cases of TCs (16.1%) arose in patients with at least one first-degree relative with diagnosis of TCs. Peculiar findings concerning hereditary lesions included the multiple presentation with an early onset age. On the basis of clinical evaluation, we propose a panel of clinical and histologic criteria for the diagnosis of hereditary TCs, which includes: (i) the diagnosis of TCs in at least two first-degree relatives or in three first- or second-degree relatives in two consecutive generations; (ii) at least one of the patients with TCs diagnosed <45 years; and (iii) the diagnosis of multiple or giant (>5-cm lesions) or rare histopathologic features (proliferating and ossifying) TCs.

Conflict of interest

The authors declare that they have no conflict of interest.

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Trichilemmal cysts (TCs), also called pilar cysts, are dermal-epithelial cysts originating from the hair follicle (1, 2). They appear as solitary or multiple intradermal palpable nodules. Histopathologically, TCs resemble the external root sheath in the region of the follicular isthmus. Proliferating and ossifying TCs are rare. Although the term trichilemma was first introduced by Headington and French (3), only 6 years later Pinkus

named the portion of the external root sheath between the bulge and the opening of the sebaceous duct as the trichilemma.

TCs show a predilection for the scalp (4). The clinical differential diagnosis includes a wide spectrum of lesions such as sebaceous and epidermoidal cysts and cylindromas. The diagnosis is easier when the clinical examination is integrated with the collection of

anamnestic personal and familial clinical data, which sometimes reveal a hereditary setting. Little is known about the frequency of the hereditary TCs. The first description of autosomal dominant (AD) TCs was provided by Munro (4) and Stephens (5). Leppard et al. reported 115 individuals from 60 families who had TCs; in 46 of these (77%) an AD pattern of inheritance was showed (1).

TRICY1 gene mutation status has been investigated for a pathogenetic role in a Danish family with 38 members, 11 of which affected by TCs (6). The authors sequenced the two candidate genes previously reported in inherited hair defects: *CTNNB1* and *MLHI*; however, they failed to detect mutations in exons and intron–exon boundaries.

In this study, we retrospectively reviewed the histopathologically proven cases of TCs excised at our Department from 1991 to 2012. We chose to investigate *PTCH1* gene because scientific literature had not provided any peculiar pathogenic evidences for the involvement of the already studied *TRICY1*, *CTNNB1* and *MLHI* genes; moreover, we had an early clinical suspicion of cylindromatosis in our first patient who had a particularly aggressive cutaneous phenotype. Such phenotype was not related to *CYLD* gene mutation, so that we decided to investigate *PTCH1* as second choice. The specific aim was to investigate the frequency of the hereditary TCs among a series of patients in a single institution and to try to elucidate the biomolecular background underlying the TCs hereditary transmission.

Materials and methods

Overall, 149 surgically excised and histologically confirmed TCs were retrospectively reviewed by consulting the archives of the University of Modena.

Family pedigrees were drawn for all probands. Written informed consent, agreeing to peripheral blood sampling and genetic analysis, was obtained. Molecular analysis of *PTCH1* was performed. The *PTCH1* cDNA sequence from GenBank was used as a reference sequence, where the A of the ATG translation initiation start site represents nucleotide +1. An Institutional Review Board approval was obtained.

Results

In our archives, we found 149 patients affected by TCs in a period of 2 decades. The population was composed of 66 males and 83 females (mean age: 50.1 ± 17.7 years). Among these patients, 76 (51%) presented multiple TCs and 73 (49%) only single lesions (Table 1).

At onset, TCs were most commonly found on the scalp (77.8%), but they also occurred in trunk (8.1%), limbs (6.7%), face (5.4%), and arms (4.7%). When located both on the scalp and on the body, the skin over the TCs presented visible telangiectasia (Fig. 1a,c). The cysts appeared between the ages of 5 and 93; the age of onset in females was 46.9 ± 16 years, whereas in males was 52.6 ± 18.6 years (Tables 1 and 2).

Table 1. Clinical features of hereditary trichilemmal cysts (TCs) patients

	Number of patients (%)	Age (mean $\pm$ SD)
Patients diagnosed with TCs	149 (100%)	50.6 ± 17.7
Female (%)	83 (55.7%)	46.9 ± 16
Male (%)	66 (44.3%)	52.6 ± 18.6
Patients diagnosed with a single TC	73 (49%)	52.9 ± 17.03
Female (%)	44 (29.5%)	53.5 ± 17.9
Male (%)	29 (19.4%)	52.2 ± 15.8
Patients diagnosed with multiple TCs	76 (51%)	47.3 ± 18
Female (%)	39 (26.1%)	51.4 ± 19.4
Male (%)	37 (24.8%)	42.8 ± 15
TC patients diagnosed with a familial form	24 (16.1%)	41.5 ± 17.3
Female (%)	13 (8.7%)	36.2 ± 16.9
Male (%)	11 (7.4%)	47.3 ± 16.6

SD, standard deviation.

Fig. 1. Clinical appearance of trichilemmal cysts (TCs) in the probands of families with hereditary TCs: (a) A proband's Pedigree; (b) and (c) B proband's Pedigree; and (d) C proband's Pedigree.

Twenty-four cases of TCs (16.1%) arose in patients with at least one first-degree relative with diagnosis of TCs. The age of onset was lower in women with a TCs familial history than in sporadic cases (Table 3). As regards the number of cysts occurring in familial settings, more than half of the patients showed a single lesion (62.5%) and multiple cysts were reported more frequently among men. Compared to their sporadic counterpart, we noticed a younger age of onset and the presence of multiple TCs among hereditary cases, whereas we did not find a peculiar body site involvement that could help in differentiating familial and sporadic cysts (Table 1). Two patients with a clinical history for familial TCs showed associated malignancies: the first patient was affected by colorectal adenocarcinoma and melanoma, whereas the second one by a renal cell carcinoma and prostate adenocarcinoma.

Table 2. Anatomical area involved in trichilemmal cysts (TCs) development

Anatomical area	First TCs (% patients)	Second TCs (% patients)	Third TCs (% patients)
Sculp	116 (77.8%)	7 (4.7%)	2 (1.3%)
Trunk	12 (8.1%)	2 (1.3%)	0
Lower extremity	10 (6.7%)	0	0
Face	8 (5.4%)	0	1 (0.7%)
Upper extremity	7 (4.7%)	1 (0.7%)	0

Table 3. Characteristics of patients with a familial inheritance of trichilemmal cysts (TCs)

	Patients with a single TC	Patients with multiple TCs
TCs patients affected by a familial form (%)	15 (10.1%)	8 (5.4%)
Age (mean $\pm$ SD)	42.3 $\pm$ 19.9	40.1 $\pm$ 13
Female affected by familial form (%)	10 (6.7%)	3 (2%)
Age (mean $\pm$ SD)	37.1 $\pm$ 18.2	35 $\pm$ 15.6
Male affected by familial form (%)	5 (3.4%)	6 (4%)
Age (mean $\pm$ SD)	52.8 $\pm$ 20.8	42.7 $\pm$ 12.2

SD, standard deviation.

Pedigree A

The proband (II.1), a 49-year-old Caucasian male, had multiple lesions of the scalp. Histopathological examination revealed TCs. The proband referred that his father too (I.1, Fig. 2) presented giant TCs of the scalp.

PTCH1 gene sequencing revealed a novel and rare germline *PTCH1* variant (exon 23; R1297Q) that we do not found in 350 control individuals. This *PTCH1* variant was detected neither in the father's cyst nor in the mother's vulvar squamous cell carcinoma. Hence, it may not be responsible for the genetic mechanism involved in the development of TC (Fig. 3).

Pedigree B

The proband (III.1 Pedigree B), a 17-year-old female, presented with TCs on her face arisen at the age of 12. Her mother (II.2), aged 59 years, had TCs on her shoulder and arm and her grandfather (I.1) had a TC on his scalp.

Pedigree C

The proband (III-1), a 27-year-old female, had TCs on her scalp. Her brother (III.2), her mother (II.2), and her grandmother (I.2) all had TCs on the scalp. The *PTCH1* variant was not detected.

Pedigree D

The proband (III.2), a 23-year-old female, had a TC on the left arm since the age of 18. Her mother (II.2) had one on her abdomen and multiple on the scalp.

Pedigree E

The proband (III.1), a 34-year-old female, showed TCs on her scalp and face. Her mother (II.2) had TCs on the scalp and neck.

Pedigree F

The proband (III.1), a 50-year-old female, developed TCs on her scalp at the age of 24. Her uncle (II.1) and her grandfather (I.1) had giant TCs on the scalp. Her parents (II.2 and II.3) did not show TCs. The *PTCH1* variant was not detected.

Pedigree G

The proband (III.1), a 63-year-old male, presented with several (>40) TCs on his scalp and arms. His mother also (II.3) showed TCs on the arms. The *PTCH1* variant was not detected.

Discussion

The familial character of TCs is unknown to most physicians, and the only genetic studies performed in the past failed to detect peculiar mutations associated to this hereditary disorder (6). The two main new evidences of this study are as follows: first, the assessment of the incidence of hereditary TCs cases among a consecutive cohort of apparently sporadic TCs patients; second, exon 23 *PTCH1* variant appears rather uncommon in TCs development.

At present, the diagnosis of a 'hereditary trichilemmal cysts syndrome' relies on a list of not well-defined criteria. Beyond the classical HTC syndrome, TCs can occur in the familial occurrence of total leukonychia, TCs and ciliary dystrophy with dominant autosomal pattern of inheritance (FLOTCH) syndrome (7) and in type 2 segmental manifestation of multiple glomus tumors in which the giant TCs show a linear distribution on the scalp (8). Hence, it is important to evaluate the clinical features associated to TCs in order to clarify the clinical background of the potential TCs hereditary disorder. An accurate clinical classification is also useful for the recruitment of a cohort of homogeneous TCs patients, which allows the investigation of the genetic mechanisms underlying an AD transmission.

Leppard et al. reported an AD transmission of the cutaneous cystic phenotype in 46 of their 60 (77%) families with hereditary TCs (1); among the 14 probands with negative family history, 5 had no knowledge of other members of their families.

In our study, we detected 16.1% patients with TCs that presented also one first-degree or two second-degree relatives affected by the same skin lesions.

Fig. 2. Seven families with hereditary trichilemmal cysts. The arrows indicate the proband.

Fig. 3. Electropherogram of the detected *PTCH1* variant (exon 23; R1297Q).

This could imply that patients presenting unusual TCs, especially when diagnosed at early age, should be carefully checked to discover underlying an unknown hereditary susceptibility. We believe that the true incidence of the syndrome may be underestimated because of the benign nature of the lesions and the absence of a careful reconstruction of the pathological family anamnesis.

We propose a panel of clinical criteria for the identification of hereditary TC cases, which includes: (i) the diagnosis of TCs in at least two first-degree relatives

or in three first- or second-degree relatives in two consecutive generations; (ii) at least one of the patients with TCs diagnosed <45 years; and (iii) the diagnosis of multiple or giant (>5 cm) or rare histopathologic features (proliferating and ossifying) TCs.

The critical role of the early onset age of TCs is shown in our study, in which 14 of 17 (82%) TCs probands aged <30 years and 27 of 55 (49%) probands aged <45 years reported a positive family history for TCs; this is confirmed by the observation of

the incidence of the positive family history in probands aged >45 years at the diagnosis (13%).

The clinical suspicion of hereditary setting allows early diagnosis and screening of these skin neoplasms even in young family members; in fact, sporadic TCs usually occur in elderly individuals. An early detection permits to avoid the risk of malignant transformation that is usually high in the context of giant TCs (8).

The *PTCH1* variant associated to our first TC familial case is interesting because it is not present in any 350 unrelated healthy Italian subjects. A peculiar genotype–phenotype correlation for *PTCH1* gene is not known, because all known mutations are located in most exons and spread all over the *PTCH1* gene (9). The exon 23 of the *PTCH1* has been rarely involved in the pathogenesis of nevoid basal cell carcinoma syndrome (NBCCS); the only exon 23 mutation reported (R1319H) (10) is in the last intracellular C-terminal domain of *PTCH1*, which was identified as an important regulatory region essential for proper signaling of Sonic Hedgehog (HH) or *PTCH1*.

Literature has already reported that the involvement of CGG triplet repeat-number polymorphism (CGG8) alleles in the 5'-untranslated region of *PTCH1* was significantly higher in the ameloblastoma (AML) patients, indicating a possible relationship between the CGG8 allele in *PTCH1* and the risk for AML. This *PTCH1* variant in patients with AMLs was not showed to be a pathogenic factor for cancerogenesis (11). In addition, Pro 1315Leu polymorphism might modulate the association between the use of oral contraceptives and breast cancer risk (12). It appears that the deletion of the last 156 amino acids is responsible for the alteration of HH signaling with a consequent reduction of its target genes. Mutational status of codon 1315 was further analyzed to evaluate its association with non-melanoma skin cancer and might be in linkage disequilibrium with other polymorphisms (13). A French study reported the role of *PTCH1* exon 23 polymorphism c.3944C4T in the development of sporadic BCC (14). Concerning sporadic trichoblastomas, no studies have showed a significant contribution of *PTCH1* mutations in their pathogenesis, so that their genetic background remains debatable (15).

TCs may be present in hereditary–familial settings, and in such cases they are multiple, with early age of onset and contemporary occurring in two or more first- or second-degree relatives. On the basis of these clinical

evaluation, we propose three clinical and histologic criteria that would allow identification of autosomal dominantly inherited TCs. Further studies are required to validate the potential role of *PTCH1* in the cyst formation both in the sporadic and hereditary setting.

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