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The significance and interpretation of congenital hypertrophy of the retinal pigment epithelium (CHRPE) diagnosed in patients with Familial Adenomatous Polyposis: A review

Paula Cristina Steffen Novelli[1], Anelise Stachewski Russo[2], Carlos Augusto Real Martinez[3] and Fábio Guilherme Campos[4]*

[1]São Francisco University, Bragança Paulista, Brazil

[2]Portuguese Hospital Benefit in Sao Paulo, Sao Paulo, Brazil

[3]Campinas State University, Campinas, São Paulo and São Francisco University Medical School, Bragança Paulista, Brazil

[4]University of São Paulo Medical School, São Paulo, Brazil

Abstract

Classical Familial Adenomatous Polyposis (PAF) is a genetic disease with autossomal inheritance related to germline mutations in the *APC* or *MUTYH* genes. Mutation carriers usually develop polyps throughout the gastrointestinal tract at the beginning of adolescence, mainly in the colon. Some of these patients may be diagnosed with some benign and malignant extraintestinal manifestations (MEI), one of them is the congenital hypertrophy of the retinal pigment epithelium (CHRPE). The present article aims to review and discuss the role of CHPE as a diagnostic marker in FAP patients. Although retinal lesions may be present since birth, family members at risk for developing FAP are usually advised to undergo screening during the second decade of life, when colonic adenomas develop. Thus, fundoscopy should be included as part of the clinical evaluation of FAP patients, especially in pediatric patients, as it is an inexpensive, non-invasive, easily accessible and enforceable exam. CHRPE is now considered a reliable clinical marker for FAP diagnosis and may in induce genetic analysis.

Introduction

Classical Familial adenomatous Polyposis (PAF) is a genetic disease with autosomal dominant inheritance related to germline mutations in the *APC* gene. Others belong to families exhibiting a recessive pattern of inheritance determined by mutations if *MUTYH* gene. PAF carriers may develop polyps throughout the gastrointestinal tract from the onset of adolescence, mainly in the colon. Those patients should undergo prophylactic colectomy to avoid development of colorectal cancer.

After the diagnosis of the "index" case, descendants should undergo clinical, endoscopic and genetic evaluation as they have a 25-50% risk of inheriting the disease. Genetic testing is now considered the more accurate tool to identify affected relatives, besides its associated cost in some countries.

Eventually, both benign and malignant extraintestinal manifestations (MEI) may be associated with this genetic disorder. Some of them are represented by cutaneous epidermoid cysts, osteomas, dental malformations, desmoid tumors, gastroduodenal adenomas, central nervous system, hepatobiliary and thyroid neoplasms [1,2]. On interesting feature is the occurrence of congenital hypertrophy of the retinal pigment epithelium (CHRPE).

The present article aims to review and discuss the role of CHPE as a diagnostic marker in FAP patients.

History and incidence

CHRPE was first described by Blair and Trempe in 1980 [3,4]. Since them, it has been considered a strong PAF marker and a common MEI, with reported incidence varying from 58 to 92%. However, this ophthalmological alteration may also be found in 1.2 to 4.4% of population.

Definition

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is a rare benign lesion of the retina, usually asymptomatic and detected at routine eye examination. It results from a proliferation of pigmented epithelial cells, well defined, flat, does not cause visual symptoms if they do not reach the macula.

These retinal changes are represented by four or more lesions (sometimes multiple), rounded, flat, bilateral hyperpigmented (Figure 1) and divided into 5 presentation groups, by the Traboulsi classification. In different studies, the presence of at least four lesions, regardless of their size, corresponds to a sensitivity close to 0.630 with maximum specificity [5].

Diagnosis is established by funduscopy, and may be supplemented with fluorescent angiography and color retinography, which also

Correspondence to: Fábio Guilherme Campos, Rua Padre João Manuel 222 Cj 120 - São Paulo, Brazil, CEP: 01411-000, E-mail: fgmcampos@terra.com.br

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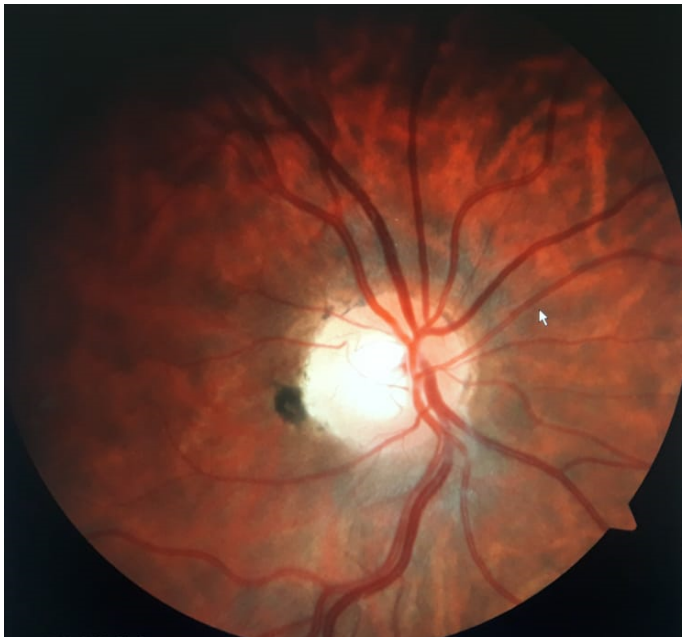

Figure 1. Retinography of patients with PAF and CHRPE. (Courtesy of the Unicamp Coloproctology Group)

contribute to the differentiation of other inflammatory, infectious and congenital chorioretinal lesions. The survey should include the most peripheral regions of the retina and all negative exams should be repeated a second time [6-8].

Clinical relevance

Family members at risk for developing FAP should be screened during the second decade of life, when colonic adenomas develop. However, it is recognized that retinal lesions may be present since birth. Thus, fundoscopy should be part of the clinical evaluation of FAP patients, especially in pediatric ones, as it is an inexpensive, non-invasive, easily accessible and enforceable exam [8,9].

Ruhswurm *et al.* [10] demonstrated that ophthalmologic exams facilitate the predictive diagnosis in FAP patients and first-degree relatives. Once diagnosed, CHRPE becomes a reliable clinical marker for the diagnosis and may facilitate genetic analysis, by directing the localization of the mutation in the gene. So, it is considered an early marker of the pre-symptomatic phase of the disease.

In families not presenting CHRPE, however, the negative ophthalmological examination has no diagnostic value. Genetic marker studies should therefore be reserved for negative CHRPE family members and for the remaining individuals who, although belonging to positive CHRPE families, have negative ophthalmologic examinations [3,4,10-17].

On the other hand, Chagas *et al.* [11] reported that CHRPE may not allow diagnosis as early as linkage analysis, since its expression also increases with age, becoming maximal during the second decade of life (when colonic polyposis also develops).

Recognition of the CHRPE phenotype allows the search of a specific mutation in a smaller coding region of the *APC* gene, generally located in exons 9-15 and between codons 463 and 1387 of the *APC* gene.

CHRPE positive individuals present a 100% chance of having the genetic mutation [2]. Intra-familial variation of CHRPE gene expression is possible, indicating that negative fundoscopy individuals belonging to CHRPE positive families should not be excluded from the colonoscopic screening and or genetic analysis.

Conclusion

Screening for CHRPE is an easy method of diagnosing patients with FAP. In conjunction with other screening methods, it allows an early diagnosis mainly in pediatric patients. Simultaneously, it also allows an easier genetic analysis, focusing on the mutation in a smaller region of the *APC* gene. CHRPE lesions are now considered a noninvasive phenotypic marker that may allow early diagnosis during family screening.

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