Diagnostic value of fundus examination in familial adenomatous polyposis

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Abstract

***Background*—Multiple, bilateral lesions of congenital hypertrophy of the retinal pigment epithelium (CHRPE) have been described in patients suffering from familial adenomatous polyposis (FAP) since 1980. This study aimed to determine a reliable diagnostic criterion, based on the size and number of retinal CHRPE lesions, allowing the screening of patient carriers of the gene responsible for FAP.**

***Methods*—32 control subjects and 144 patients belonging to 85 FAP families were studied, divided into 124 carriers of the genetic alteration and 20 non-carriers.**

***Results*—In carriers of the deleted gene, multiple, bilateral retinal lesions were consistently observed. Lesion situation, size, shape, and degree of pigmentation were variable however. A positive criterion for FAP was defined as the presence of at least four lesions whatever their size, or at least two lesions one of which is large. This criterion showed a high sensitivity (0.68) and a maximal specificity (1). Within each family, the retinal phenotypic expression was homogeneous. CHRPE lesions were observed in two thirds of the FAP families and absent from the remaining third.**

***Conclusion*—By using this new positive diagnostic criterion, fundus examination allows early detection of those children carrying the gene responsible for FAP in families positive at ocular examination.**

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Familial adenomatous polyposis (FAP) is an autosomal dominant disease, the diagnosis of which is made on the presence of more than 100 adenomatous polyps in the colon and rectum. These adenomata generally appear at puberty and their malignant change is unavoidable without prophylactic total colectomy. The gene responsible for FAP, called the adenomatous polyposis coli (APC) gene, was localised to the long arm of chromosome 5 (5q21-q22) in 1987 and cloned in 1991.[1 2] The development of extracolonic manifestations in FAP has, since 1953, been termed Gardner's syndrome.[3 4] In spite of unexplained variation of the expression of these extracolonic lesions, no study has shown genetic heterogeneity between the different clinical forms, which are now considered phenotypic variations of the same disease.[5–7] These extracolonic manifestations are proliferations of different tissues, and frequently include duodenal tumours and desmoid tumours.[8]

Since 1980, the existence of multiple, bilateral lesions of congenital hypertrophy of the retinal pigment epithelium (CHRPE) has been reported in patients affected by FAP.[9–15] These retinal lesions, notable for their frequency, are asymptomatic and have no malignant potential. Their number, shape, size, situation, and pigmentation are variable, but multiple lesions are a constant finding. Their ophthalmoscopic characteristics are identical to the isolated lesions of CHRPE observed in the general population.[16–19] The aim of this study was to define reliable positive criteria on examination of the fundus with optimal sensitivity and specificity.

Methods

PATIENTS

Between 1990 and 1993, 144 patients belonging to 85 FAP families were examined by the same ophthalmologist (AT). An FAP family was defined by at least one single affected member. The status of each patient was established by clinical examination, colonoscopy, and molecular analysis of the APC gene. Among the 144 patients, 124 were affected and 20 unaffected by FAP.

As a control group, 32 subjects, who did not belong to a FAP family, received a fundus examination; 30 of these had a hereditary non-polyposis colorectal cancer (the HNPCC syndrome), one had a Peutz–Jeghers syndrome, and one had a hyperplastic polyposis.

At the time of examination, the ophthalmologist was not informed of the status of affected or non-affected patients, or control subjects.

OPHTHALMIC EXAMINATION

The ophthalmic examination was performed with a Goldmann lens after maximal dilatation of the pupil in all the adults and children more than 8 years old. In younger children, the fundus was examined with a Schepens binocular ophthalmoscope or Volk lenses. For each eye examined, a diagram was produced specifying the number, size, situation, shape, and degree of pigmentation of the CHRPE lesions. Size of the lesion was defined as small or large, depending on whether its surface was greater or less than a quarter of the surface of the optic disc (diameter of the optic disc measuring 1500 μm). The situation was specified at the posterior pole when the lesion was within the temporal arcades or in the periphery when it was beyond the temporal arcades. The shape

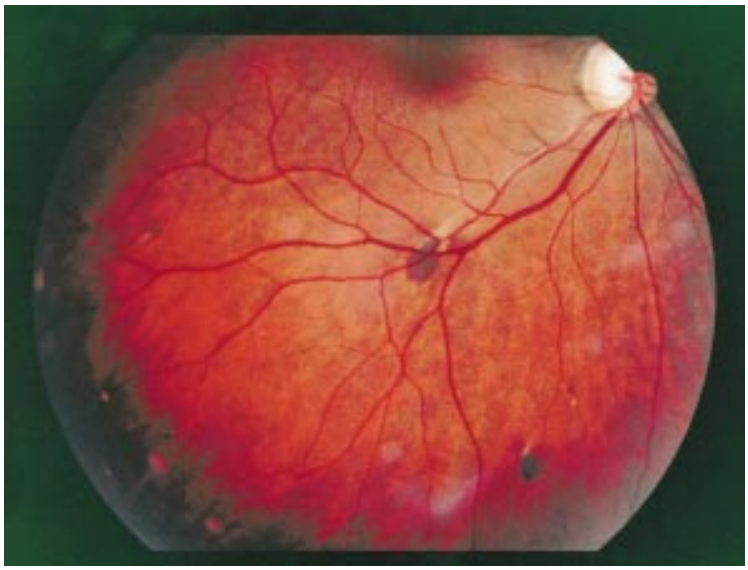

Figure 1 Fundus photography of congenital hypertrophy of the retinal pigment epithelium (CHRPE) lesions. Two large and four peripheral punctiform CHRPE lesions.

was punctiform, rounded, oval, or linear. Concerning the degree of pigmentation, the lesions appeared pigmented, depigmented, or heterogeneous (containing areas of pigmentation and depigmentation). Retinal photographs were taken when possible.

Results

DESCRIPTION OF THE LESIONS

Among the 124 FAP affected patients examined, the sex ratio was 1 (62 women and 62 men). The average age was 30.9 (range 13 months to 69.8 years). One or more retinal lesions were observed in 107 patients out of these 124 patients. The lesions were generally multiple, with an average of seven in the two eyes, varying from one to 23 (Fig 1). In 80 patients, lesions were observed bilaterally. No significant difference (paired Student's *t* test) was noted in the numbers of lesions between the right and left eye. The lesions were more frequent peripherally than at the posterior pole (84% and 16%, respectively). Most lesions (56%) were small. The large lesions were found preferentially at the posterior pole. Regarding the shape, 39% of the lesions were rounded or oval, 56% of the lesions punctiform, and 5% linear. Most lesions—that is, 76%, were pigmented, 10% depigmented, and 14% heterogeneous. The punctiform lesions were always pigmented; the large lesions were divided into 46% pigmented, 21% depigmented, and 33% heterogeneous.

Retinal lesions were observed in four out of the 20 unaffected patients belonging to FAP families. Each of them had a single lesion.

In the controls, retinal lesions were observed in only five subjects out of the 32 controls and the total number of lesions was not greater than three. These lesions were peripheral, small, punctiform, and pigmented.

SENSITIVITY AND SPECIFICITY

Several analyses were performed according to the laterality, the number, and the size of the lesions, as shown in Table l. Eighty FAP affected patients out of 124 were affected bilaterally, and one control out of 32. The specificity for this criterion was thus 0.969 and the sensitivity was 0.645. At least four lesions were found in 75 carriers and in none of the controls. The specificity for this criterion was thus 1 and the sensitivity 0.605. At least three lesions were found in 80 carriers out of 124 and in one control out of 32. The specificity for this criterion was thus 0.969 and the sensitivity 0.645.

Table 1 Sensitivity and specificity according to positive criteria

Positive criteria	*Sensitivity*	*Specificity*
Bilateral lesions	0.645 (80/124)	0.969 (31/32)
At least 2 lesions	0.742 (92/124)	0.906 (29/32)
At least 3 lesions	0.645 (80/124)	0.969 (31/32)
At least 4 lesions	0.605 (75/124)	1 (32/32)
At least 4 lesions, whatever their size, or at least 2 lesions, one of which is large	0.677 (84/124)	1 (32/32)

We defined a new criterion as the presence of at least four lesions whatever their size, or two lesions at least one of which is large. This criterion was present in 84 carriers and in no controls. The specificity of this criterion was thus 1 and the sensitivity 0.677. The positive predictive value—that is, the proportion of carriers of the APC gene among all the individuals having a positive fundus examination, equalled 1. There were no control subjects with a positive fundus examination.

HOMOGENEITY WITHIN FAMILIES

Among the 85 FAP families who were examined, 26 had at least two patients affected by polyposis. In 17 of these 26 families, the examination of the fundus was positive in the 41 affected patients. In eight families, no characteristic lesion was observed in the 18 affected patients. There was one family in which one of the three affected patients had three punctiform lesions and thus did not fulfil the positive criterion on fundus examination.

Discussion

In 1980, Blair and Trempe described the existence of CHRPE lesions in three patients affected with FAP.[9] These lesions have the same clinical and angiographic characteristics as the isolated lesions of CHRPE described first by Reese and Jones in 1956.[20 21] They are flat, with sharply defined borders, and most often oval. They can be pigmented, depigmented, or heterogeneous. Their size is variable: they can be punctiform or measure several disc diameters. They can be present all over the retina, though the large lesions are preferentially localised within the equator.[22–24] No preferential arrangement by quadrant is found. The punctiform lesions are generally peripheral or satellites of bigger lesions. According to form and pigmentation, lesions are frequently oval, pigmented with areas of depigmentation encircled by a fine greyish halo. This kind of lesion, oval and heterogeneous, is the most specific appearance in FAP patients. The lesions of CHRPE are congenital since they

have been observed in the newborn and even in a premature baby born at 7 months.[25] In this series, the youngest affected patient examined was 13 months old and showed four retinal lesions on fundus examination. Some modifications of pigmentation and size have been described in the isolated lesion of CHRPE,[26–28] but no study has documented an increase in the number of lesions in the course of familial adenomatous polyposis. Several histological studies have stated that these lesions were hamartomatous lesions of retinal pigment epithelium, in which the hypertrophied cells are arranged in several layers, associated with an increase in number and size of melanin granules, a thickening of Bruch's membrane, and an alteration of the subjacent photoreceptors.[29–31]

A single or atypical lesion may be difficult to differentiate from a choroidal melanoma or naevus, a chorioretinal scar from toxoplasma, or a secondary hyperplasia of the retinal pigment epithelium.[32–34] However, the clinical picture and a family history of adenomatous polyposis should make the diagnosis clear. In view of the multiple, bilateral character of the retinal lesions observed in FAP, they can be considered a clinical marker of the illness, defined by sensitivity and specificity. A number of authors have confirmed the high specificity (close to 1) of these retinal lesions but with a lower and more variable sensitivity (between 0.6 and 0.8).[12 22 23 35 36] Until now no hypothesis has been proposed to explain the absence of retinal lesions in 20–40% of the FAP patients.

The diagnostic criteria have been developed progressively since the initial study of Traboulsi *et al* in 1987,[14] which acknowledged as a positive criterion the presence of more than four lesions whatever their size in two eyes. In different studies, the presence of at least four lesions whatever their size corresponds to a sensitivity close to 0.630 with maximal specificity.[12 14 37] Fluctuating sensitivities (0.518 to 0.903) and a lower specificity were obtained in the patients with bilateral lesions.[14 22 24 35 37]

No statistical study has established until now the best combination of factors which can be used as a diagnostic criterion. We have evaluated the data from the individual retinal examinations according to the bilateral nature of the lesions, the number, and the number combined with the size. The existence of at least four lesions whatever their size and the bilateral character of the lesions corresponds to a sensitivity and a specificity equivalent to the data in the literature. A higher sensitivity for a specificity of 1 is obtained by the combination of the number and the size of the lesions. Thus, the presence of at least four lesions whatever their size or at least two lesions of which one is large constitutes the best diagnostic criterion of the examination of the fundus in patients affected by FAP.

Since 1984, several authors have observed that multiple retinal lesions were present in about two thirds of families affected by adenomatous polyposis and that they were absent or fewer in nearly a third of the families.[11 12 24 37 38] In our study, there were 41 patients from 17 of the 26 families where several patients affected by adenomatous polyposis were examined, who all had positive fundus examinations according to our diagnostic criterion. No member of eight other families had a lesion. In one family, from which five members were examined, there was a discrepancy between the examination of the fundus and the genetic status. The retinal examination of an affected 13-year-old child had only three peripheral punctiform lesions. The examination, although carried out with a Goldmann lens, could have missed a lesion. With the exception of this family, the presence or absence of retinal lesions was a familial characteristic, and the families can be divided into two groups—those in which all the affected patients are positive on fundus examination and those in which all the affected patients are negative on fundus examination.

In the families negative on examination, screening of FAP affected patients by ophthalmoscopic examination is not helpful. In the families positive, examination of the fundus can be used to make a predictive diagnosis from a young age. Mutation analysis of APC gene is now possible in most of FAP families. The study of the structural alterations of the APC gene, responsible for FAP, has contributed to the understanding of the CHRPE expression.[1 39–41] Thus, a direct correlation between the constitutional causal mutation and the retinal expression appears when the position of the mutation on the APC gene is taken into account. The retinal lesions are only present if the mutation is located between codons 463 and 1387 of the APC gene.[42] So, knowledge of CHRPE phenotype allows the focused research of the mutation on a smaller coding region of the APC gene.[42 43] Especially, mutation de novo can be detected more easily when retinal phenotype is known.[44] The important heterogeneity between families and the homogeneity within families of the retinal phenotype are explained by the situation of constitutional mutations of the APC gene in each family. Last genetic studies have demonstrated that CHRPE expression depends on the length of abnormal protein produced by defected APC gene.[43]

In conclusion, the definition of a reliable positive criterion, determined at fundus examination and based on the size and number of CHRPE lesions, rests on the study of a large series of patients affected by adenomatous polyposis from a significant number of independent families. This criterion necessitates the presence of at least four lesions whatever their size or at least two lesions of which one is large. It has been found in 68% of the patients affected by adenomatous polyposis without any false positives. The patients who were positive on fundus examination were distributed between two thirds of the families, the remaining third made up of affected patients all being negative on fundus examination. Simple, non-invasive, reliable, and reproducible examination of the fundus allows early screening, before the age of the first colonoscopy, of

children who are carriers of the affected gene, the only condition being that they are part of a family positive on fundus examination. Moreover, the information provided by fundus examination plays an important part in the management of genetic detection of constitutional APC mutations.

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