

The eye in cystic fibrosis

I. CASTAGNA, A.M. ROSZKOWSKA, F. FAMÀ, S. SINICROPI, G. FERRERI

Institute of Ophthalmology, University of Messina, Messina - Italy

PURPOSE. *To investigate modifications of ocular surface and lens transparency in patients with cystic fibrosis in relation to the stage of digestive insufficiency.*

METHODS. *Forty consecutive patients with cystic fibrosis and 24 age- and sex-matched healthy volunteers were examined. The tear tests (Schirmer's basic test, tear film break-up time) and conjunctival exfoliative cytology (CC) were used to study the ocular surface. The lens transparency was measured with the Opacity Lens Meter 701 (OLM 701, Interzeag AG, Switzerland). Digestive insufficiency was evaluated by the steatocrit method.*

RESULTS. *Significant changes in conjunctival cytology and lens opacity, and abnormal tear tests were detected in CF patients; the alterations were more pronounced in patients with severe digestive insufficiency.*

CONCLUSIONS. *Cystic fibrosis patients present ocular surface abnormalities and lens transparency modifications and their severity is related to the digestive insufficiency. Simple, rapid and non-invasive tear tests and cytological procedures might be used as additional tests for assessing the severity of cystic fibrosis. (Eur J Ophthalmol 2001; 11: 9-14)*

KEY WORDS. *Cystic fibrosis, Genetic disease, Tear secretion, Conjunctival cytology, Opacity lens meter, Cataract*

Accepted: July 10, 2000

INTRODUCTION

Cystic fibrosis (CF) is a fairly common lethal disease, inherited by an autosomal recessive pattern. The defect is due to a chromosomal mutation in the middle of the long arm of chromosome 7 (1, 2). CF is marked by increased viscosity of mucus secretion and a high salt concentration in exocrine secretions. Clinically, there are chronic pulmonary changes, chronic pancreatic deficiency and obstructive pathology of the gastrointestinal tract (2). Plasma concentrations of vitamin A are often low in patients with CF. This deficiency appears to be secondary to an abnormality in vitamin A secretion by the liver, abnormal vitamin A transport to extra-hepatic tissues, and reduced vitamin A absorption because of the digestive insufficiency. The clinical manifestations can be related to the abnormal mucus secretion.

A high concentration of sodium chloride in the sweat

is typical of CF, which is therefore frequently diagnosed with the sweat test (2). The malabsorption of fat in CF, an important cause of malnutrition, is commonly evaluated with the acid steatocrit method (3-5). Several clinically evident ocular complications of CF, such as xerophthalmia, functional deficiencies of the optic nerve, papilledema, nyctalopia, retinal hemorrhages and edema have been described (6-11). Ocular surface abnormalities such as goblet cell loss, enlargement of epithelial cell and keratinization were detected in experimental vitamin A deficiency (12).

Ocular surface modifications in CF have a special interest in clinical practice. Patients may complain of dry eye symptoms and fitting contact lenses call for particular attention.

In the present study we investigated the ocular surface modifications and lens transparency in patients with cystic fibrosis, correlating the results with the severity of digestive insufficiency.

METHODS

Forty consecutive patients with CF (24 females and 16 males) were studied. The age ranged from 5 to 34 years (mean 13.5 ± 11). Patients with severe pulmonary and respiratory complications, or diabetes, were excluded. As a control group 24 age- and sex-matched healthy volunteers recruited from the general ophthalmology clinic population were examined. Informed consent was obtained from adults and from the parents of children. Each patient received thorough eye examination including visual acuity, slit-lamp biomicroscopy with fluorescein staining, Goldman's or Perkins applanation tonometry and ophthalmoscopy. None had clinical evidence of corneal or lens opacities by slit-lamp examination, or other ocular or systemic disease. Four patients had punctate corneal epithelial defects positive on fluorescein staining.

The ocular surface was studied with the 5-minute Schirmer's basic tear test, tear film break-up time test (BUT) and conjunctival exfoliative cytology (CC). The CC procedure was performed after instillation of two drops of 0.4% oxybuprocaine. Specimens were obtained by conjunctival scraping with a Desmarres spatula and were collected from the inferior tarsal conjunctiva 3 mm from the lid margin, to avoid normal keratinized epithelial cells. The specimens were fixed in alcohol 95% and stained with Papanicolaou-PAS.

The specimens were examined with light microscopy at 200 x. Goblet cell density was determined as the mean of the cell counts in four high-power microscopic fields.

Specimens were classified in four cytological groups according to three-step modifications of the conjunctiva in the process of squamous metaplasia (loss of goblet cells, cellular stratification and keratinization) (Tab. I). Lens transparency was evaluated

with the Opacity Lens Meter 701 (OLM 701, Interzeag AG, Switzerland). Five consecutive measurements were taken in each eye and the mean was calculated. Digestive insufficiency was evaluated by the steatocrit method, and classified quantitatively: 1+ (ligh), 2+ (moderate), 3+ (severe).

The results in CF patients were compared to the normal values from the control group.

Statistical analysis was done using Fisher's exact test to analyze CC data and Student's t-test to compare the tear test and lens transparency values.

RESULTS

All CF patients had normal or best corrected visual acuity of 20/20. Eleven patients had a myopic and five a hyperopic refractive defect. Ophthalmoscopic findings were normal in all patients. Applanation tonometry values ranged from 12-18 mmHg (mean 15 ± 2 mmHg). The patients were divided into four groups in relation to the CC changes, using Tseng's classification (13).

The first group comprised eight patients (20%) with a normal or increased number of goblet cells, without keratinization (stage 0 of Tseng) (Fig. 1). The second group comprised 13 patients (32.5%) whose conjunctival changes were rated as stage 1 and 2 of Tseng's classification (early or moderate loss of goblet cells without keratinization) (Fig. 2). The third group comprised 14 patients (35.0%) with marked or total loss of goblet cells and mild keratinization (Fig. 3). Five subjects (12.5%) were in the fourth group, with no goblet cells and advanced conjunctival keratinization (Tseng's 4th and 5th stages) (Fig. 4).

Table II shows the goblet cell density and the tear test and lens transparency values in the patients and normal controls, with the steatocrit scores for the CF group.

TABLE I - STAGING OF CF IN RELATION TO THE CONJUNCTIVAL ALTERATIONS

Stage	Goblet cells	Cellular stratification	Keratinization
I	Increased	Normal	Absent
II	Early or mild decrease	Mild	Absent
III	Marked decrease or absent	Moderate	Mild or moderate
IV	Absent	Severe	Severe

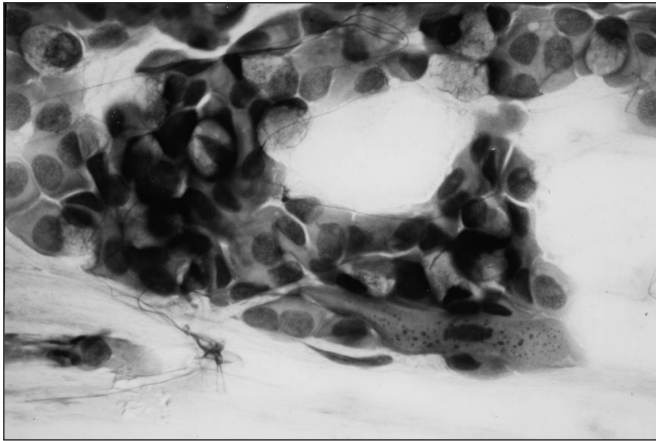


Fig. 1 - Conjunctival specimen with increased number of goblet cells (large, PAS-positive cells) and increased mucus in a patient with cystic fibrosis with early conjunctival modifications (stage I). PAS-Papanicolau staining, light microscopy 200x.

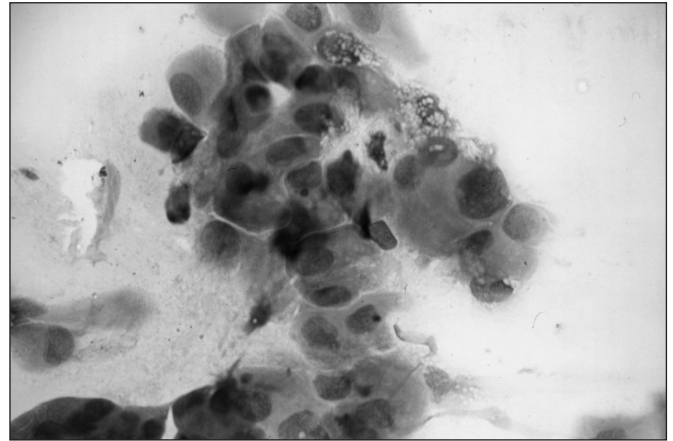


Fig. 2 - Conjunctival specimen from a patient with mild cystic fibrosis shows a moderate loss of goblet cells without keratinization (stage II). PAS-Papanicolau staining, light microscopy 200x.

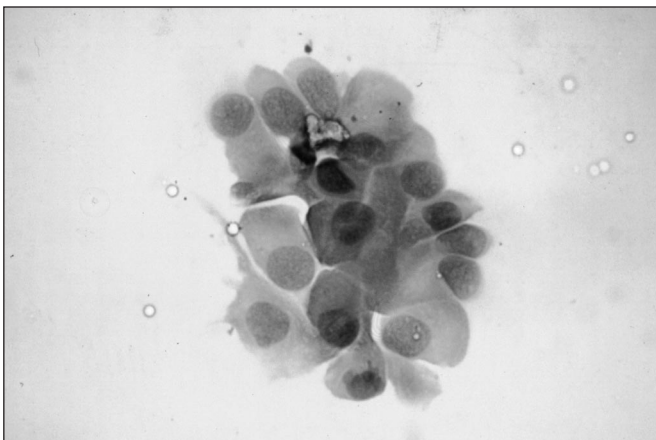


Fig. 3 - Conjunctival specimen with stage III cytological modifications shows marked loss of goblet cells with mild keratinization. PAS-Papanicolau staining, light microscopy 200x.

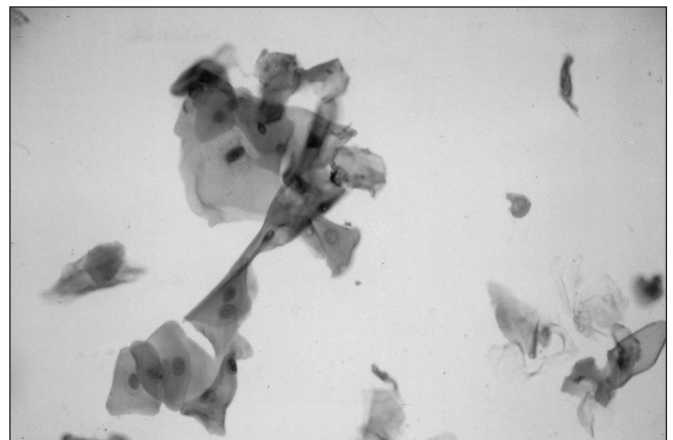


Fig. 4 - Conjunctival specimen from a patient with severe digestive insufficiency shows advanced keratinization, and total absence of goblet cells stage IV. PAS-Papanicolau staining, light microscopy 200x.

TABLE II - CONJUNCTIVAL CYTOLOGY, TEAR TEST AND LENS OPACITY IN CF PATIENTS AND IN THE CONTROL GROUP, IN RELATION TO THE SEVERITY OF THE DISEASE, ON THE BASIS OF THE STEATOCRIT

Number of patients (%)	Conjunctival cytology	Number of goblet cells x field	Schirmer's basic test (mm)	BUT (sec)	OLM 701	Steatocrit (%)		
						1+	2+	3+
8 (20.0%)	I stage	12.8 ± 2	22.2 ± 5	18.4 ± 3	12.30 ± 0.5	100		
13 (32.5%)	II stage	8.5 ± 1	16.3 ± 3	15.8 ± 2	16.40 ± 0.3	7.7	76.9	15.4
14 (35.0%)	III stage	3.6 ± 2	4.8 ± 3	11.8 ± 3	17.70 ± 0.2		15.8	84.2
5 (12.5%)	IV stage	0	4.2 ± 2	10.2 ± 2	17.90 ± 0.6		20.0	80.0
24 (100%)	Normal	10.6 ± 2	18.7 ± 6	16.1 ± 2	8.25 ± 0.5			

TABLE III - MEAN LENS TRANSPARENCY IN CF PATIENTS AND CONTROLS, MEASURED WITH THE OPACITY LENS METER 701

	CF patients	Control group	Statistical significance
OLM 701	15.40 ± 1.4	8.25 ± 0.5	p < 0.01

Schirmer's basic test value was lower than controls in group II, but it was still in the normal range (>5). Schirmer's values were lower than 5, considered pathological, in 19 patients from groups III and IV, with advanced conjunctival changes. This reduction was statistically significant (p<0.05). BUT was normal or increased in 21 patients from groups I and II, and significantly lower in 19 patients from groups III and IV compared to the control group (Tab. II).

Goblet cell density showed an increase in the first stage of conjunctival modifications (Tab. II). Groups II, III and IV had progressively fewer goblet cells.

The lens opacity values in group I, with slight digestive insufficiency, was 12.30 ± 0.5 (Tab. II). In group II with a higher steatocrit, it was higher, and rose further in groups III and IV. The differences in lens transparency in the four groups were significant (p<0.05).

The ocular surface and lens transparency abnormalities detected in CF patients were correlated to the steatocrit score. Patients with severe digestive insufficiency with steatocrit 3+ were more likely to have abnormal CC (p<0.01). The mean lens transparency calculated in CF patients was significantly higher than in the control group (p<0.001) (Tab. III).

DISCUSSION

None of the CF patients presented severe clinical manifestations such as pulmonary emphysema or bronchopneumonia that are frequently associated with retinal or optic nerve alterations such as hyperemic or hazy discs, increased venous tortuosity or retinal hemorrhages (6-9). The optic nerve abnormalities described in CF patients are attributable to the chloramphenicol therapy frequently used in this condition (14, 15). The participants in this study did not receive

chloramphenicol, which might explain the absence of optic nerve complications. The study did find that CF patients may have ocular surface abnormalities such as reduced tear secretion, CC abnormalities and reduced lens transparency compared to normal subjects. Reduction of goblet cells is a sensitive indicator of ocular surface disease. This is related to the digestive insufficiency and indirectly to the subsequent low plasma concentration of vitamin A. This relation was detected by Hatchell and Sommer (12) who in their experimental study observed a strong correlation between ocular surface abnormalities with goblet cell loss and epithelial cell enlargement, and serum vitamin A levels.

Sheppard (16) found CF patients had a significantly low Schirmer result, with consecutive aqueous and lipid tear film deficiencies and a reduction in tear lysozyme, an important parameter for tear gland function. This author described a normal conjunctival epithelial cell morphology in the sample, but had some technical difficulties in performing impression cytology. Holm and Kessing (17) found goblet cells were qualitatively and quantitatively normal in patients with CF, but this may be due to the increased cell count in stage I of the conjunctival modifications, as results from our study. Rolando (18) reported differences in ferning patterns between normal and CF patients and suggested there might be physical and chemical alterations of mucins as a result of the altered relationship between mucus electrolytes and glycoproteins. There are other reports of conjunctival xerosis in CF patients (7, 8, 11).

In the present study, stage I conjunctival modifications with an increase in goblet cells and normal cellular stratification were observed in patients with light steatocrit. In this stage the tears tests were normal.

Stage II cytological modifications were detected in 76.9% of patients with moderate steatocrit, in 7.7% of those with early CF and in 15.4% with severe digestive insufficiency. The mean tears test values were lower than in the control group but the differences were not significant.

Stage III and IV severe cytological alterations were observed in patients with advanced digestive insufficiency with steatocrit 3+. In these stages the Schirmer and BUT tests gave significantly lower values than controls (p<0.05), indicating respectively eccrine abnormalities and dysfunction of goblet cells.

The severe keratinization detected in advanced CF with severe digestive insufficiency might be an indirect sign of low serum vitamin A concentrations, as reported by Hatchell (12). This author indicated the usefulness of impression cytology as a screening tool for detecting early xerophthalmia due to vitamin A deficiency. The present study found ocular surface modifications and a reduction in lens transparency in CF patients, highlighting the relations between these changes and the digestive insufficiency. The reduction of lens transparency might be related to the low concentration of vitamin A in serum, often found in patients with CF.

Several studies suggest that cataract is associated with the availability of vitamins and minerals (19-21). The risk of some cataract types is decreased in relation to an adequate intake of vitamins A, C and E. A low concentration of vitamin A in the aqueous humor might lower the ascorbic acid concentration in the aqueous humor and lens, and this may precipitate cataract. Vitamin A deficiency alters the mucopolysaccharide metabolism and leads to stabilization of lysosome-8-containing acid hydrolytic enzyme and to edema in the ciliary body. These two factors may lead to a lowering of the acid concentration in the aqueous humor. Vitamin A causes lability of lysosomal membranes, resulting in the release of hydrolytic

enzymes into the ciliary epithelium, and this release activates the transport of ascorbate to the aqueous humor (20).

An understanding of the role of glycoprotein and electrolyte changes in the CF lens might clarify the exact role of antioxidants in cataractogenesis. The ophthalmologic care of CF patients could have an important role in the overall clinical management. Supplementary therapy with artificial tears might be recommendable in advanced stages of the disease. Fitting contact lenses in CF patients needs particular attention, with frequent ophthalmological controls.

The simple, rapid, relatively non-invasive and repeatable qualitative and quantitative tear tests and conjunctival exfoliative cytology are useful for the diagnosis of dry eye in early CF. Future investigations may confirm the validity of these testing methods as an indirect help in establishing the need for vitamin A supplements in these patients.

Reprint requests to:
Irene Castagna, MD
Institute of Ophthalmology
Policlinico Universitario
Via Consolare Valeria
98100 Messina, Italy

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