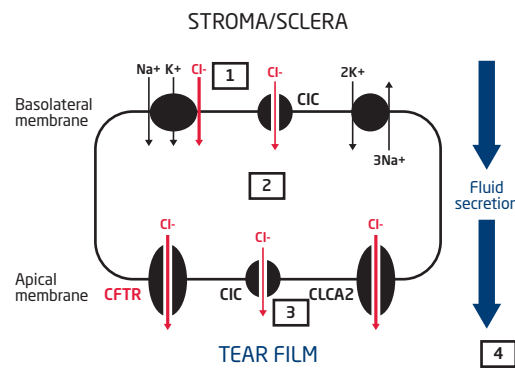


# The ocular associations of cystic fibrosis

**Katharine Evans, Rachel North and Christine Purslow** discuss the ocular complications of the disease cystic fibrosis. C6390, one general CET point, suitable for optometrists and DOs

Cystic Fibrosis (CF) is one of the most common, life-threatening inherited diseases in Caucasians,<sup>1</sup> currently affecting over 7,500 individuals in the UK.<sup>2</sup> CF is characterised by lung disease,<sup>3</sup> a high sodium chloride concentration within the sweat<sup>4</sup> and CF-Related Diabetes (CFRD). Other features include male infertility<sup>5</sup> and pancreatic insufficiency which can ultimately lead to malnutrition.<sup>6</sup> This autosomal recessive disease is caused by a defective membrane protein known as cystic fibrosis transmembrane conductance regulator (CFTR).<sup>7</sup> To date, more than 1,000 mutations of the CF gene have been identified.<sup>8</sup> CF displays extensive variation in both genotype and phenotype depending how severely the mutation disrupts CFTR function and synthesis.<sup>9</sup> Located within the apical membrane of various epithelia, such as the pancreas and the lung, the primary function of CFTR is to regulate the flow of chloride ions (Cl<sup>-</sup>).<sup>10</sup>

Treatment for the disease takes many different routes including: physiotherapy,<sup>11</sup> pancreatic enzyme replacement therapy,<sup>6</sup> vitamin supplementation,<sup>12</sup> appropriate nutrition<sup>13</sup> and pharmaceutical treatment to control respiratory infection and inflammation.<sup>3</sup> Gene and protein repair therapy, which aim to correct abnormal CFTR function, remain promising for future therapy.<sup>14, 15</sup> However, currently organ transplantation is the only definitive treatment for CF.<sup>16</sup> The major cause of death is progressive pulmonary disease which is complicated by respiratory infection.<sup>8</sup> However, life expectancy continues to increase; in 1964 survival was only five years of age, however in the UK in 2002, 11 per cent of the CF population are over 30 years of age.<sup>17</sup> In the US, the median survival rate rose to 36.5 years of age in 2005<sup>18</sup> and with contemporary CF management and research, life expectancy continues to increase. As a consequence, eye care practitioners are more likely to encounter patients with CF and need to be aware of the



**Figure 1** Diagram of a simplified corneal/conjunctival epithelial cell (1) Cl<sup>-</sup> enters the cell from the stroma via NKCC (Na<sup>+</sup>/K<sup>+</sup>/2Cl<sup>-</sup> co-transporter) and possibly ClC channels (voltage gated Cl<sup>-</sup> channels). (2) Intracellular Cl<sup>-</sup> levels are raised above equilibrium. (3) Cl<sup>-</sup> is secreted into the tear film via CFTR, CLCA2 (calcium activated Cl<sup>-</sup> channels) and possibly ClC channels. (4) Fluid is secreted into the tear film via osmosis

**TABLE 1**

#### Morphological differences in the CF corneal endothelium<sup>49</sup>

- Reduced endothelial cell area
- Increased corneal thickness
- Increased endothelial cell density
- Increased endothelial cell permeability
- Increased relative endothelial pump rate

common ocular associations of CF.

More recently, CFTR has also been discovered in various ocular structures, including the corneal epithelium,<sup>19</sup> corneal endothelium,<sup>20</sup> conjunctival epithelium<sup>21</sup> and the retinal pigment epithelium (RPE).<sup>22</sup> Cl<sup>-</sup> movement via ion channels such as CFTR is critical for various aspects of ocular physiology. In the corneal and conjunctival epithelium, active Cl<sup>-</sup> transport contributes to basal tear production<sup>23,24</sup> and in the corneal endothelium, Cl<sup>-</sup> efflux facilitates the preservation of corneal transparency.<sup>25</sup> In the RPE, Cl<sup>-</sup> movement contributes to the regulation of the subretinal space and normal RPE cell integrity.<sup>26</sup> In patients with CF, Cl<sup>-</sup> transport via CFTR may be defec-

tive or completely absent. Therefore, all of these functions are likely to be compromised, the severity of which may be dictated by the severity of the CF mutation.

#### Ametropia and binocular vision anomalies

Unfortunately there has been no large-scale assessment of ametropia and binocular vision status of CF children. CF babies are frequently of a low birth weight<sup>27</sup> which itself is associated with a higher incidence of ametropia, strabismus and amblyopia.<sup>28</sup> This indicates the importance of early and regular eye examinations for all children with CF.

#### The tear film and ocular surface

While it is agreed that stimulated tears are secreted from the lacrimal gland, the basal tear film was believed to be secreted from the accessory glands of Krause and Wolfring.<sup>29</sup> However, recent research indicates that fluid secretion secondary to active ion transport by the corneal and conjunctival epithelium is responsible for basal tear production.<sup>23,30,31</sup> Cl<sup>-</sup> transport via CFTR, present in the corneal and conjunctival epithelium, is likely to be critical to establish the high osmotic gradient in order for fluid to enter the tear film (Figure 1). Therefore CF patients, with defective Cl<sup>-</sup> transport from the ocular epithelia are likely to suffer from aqueous deficient dry eye as a result of abnormal basal tear production.

A number of clinical studies of subjects with CF have observed abnormally low tear secretion levels with Schirmer's test in 29-81 per cent of patients.<sup>32-35</sup> Abnormal fluorescein tear break up time has similarly been observed in 49-54 per cent of CF subjects.<sup>33,36</sup> Ocular surface staining, indicating a loss of epithelial cell integrity, has been observed in numerous studies. Corneal fluorescein staining was present in 60-82 per cent of CF patients.<sup>32,37</sup> Conjunctival rose bengal

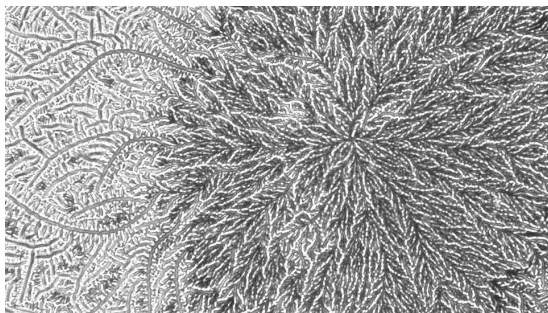


Figure 2a Normal tear ferning pattern

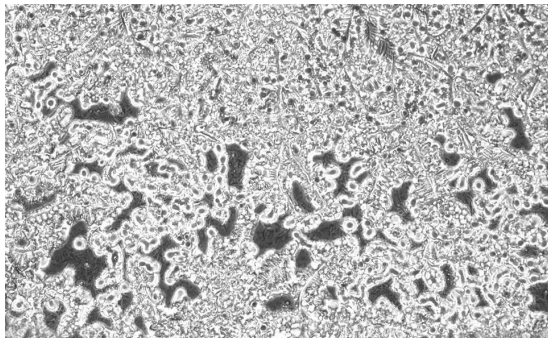


Figure 2b Abnormal tear ferning pattern observed in dry eye

staining (RBS) however was observed in 23-29 per cent.<sup>32,33</sup>

Tear ferning is a technique where small tear samples are dried onto a microscope slide and viewed under high magnification and graded according to their appearance (Figure 2a).<sup>38</sup> This technique can be used to assess the quality of the tear film and indicate the presence of dry eye (Figure 2b).<sup>39</sup> Significantly higher levels of abnormal tear ferning have been observed in two separate clinical studies of CF patients, indicating a high incidence of dry eye.<sup>40,41</sup>

Cytokines are a group of signalling molecules which mediate the immune response.<sup>42</sup> Various cytokines are up-regulated in the tear film of patients with dry eye<sup>43</sup> and Sjögren's syndrome,<sup>44</sup> suggesting they could promote ocular inflammation in such conditions.<sup>45</sup> A number of cytokines have been found in higher concentrations in the tear film of CF subjects, indicating sub-clinical levels of ocular surface inflammation.<sup>46,47</sup>

With the discovery of CFTR in the corneal and conjunctival epithelium and its contribution to basal tear secretion, these findings indicate dry eye is likely to be a primary ocular manifestation of CF. Therefore practitioners should investigate the signs and symptoms of dry eye in all patients with CF, especially those currently wearing or considering contact lenses, in order to advise and manage these patients accordingly.

fore contributes to the maintenance of normal corneal regularity (Figure 3). As a consequence, CF patients with defective Cl<sup>-</sup> transport from the endothelium have the potential to exhibit defective corneal endothelial integrity and reduced corneal transparency.

A number of morphological differences have been observed in the corneal endothelium of CF patients (Table 1).<sup>49</sup> Interestingly, these findings were made long before the detection of CFTR in the corneal endothelium and its contribution to the maintenance of corneal transparency. Such differences suggest adaptation or compensatory measures by the CF corneal endothelium in response to defective Cl<sup>-</sup> transport via CFTR. Unfortunately, as corneal transparency was not recorded, it is unclear if the morphological differences have allowed for full compensation. Therefore, examination of the corneal endothelial integrity is essential in CF patients, especially those wearing contact lenses.

**Xerophthalmia**

Xerophthalmia refers to the group of ocular conditions related to Vitamin A deficiency.<sup>50</sup> Vitamin A deficiency is a common characteristic of CF, caused by impaired absorption of the fat-soluble vitamin.<sup>51</sup> Manifestations include night blindness, corneal and conjunctival xerosis (drying).<sup>52</sup> Provided the deficiency has not been too severe or prolonged, the effects can be typically reversed following appropriate vitamin A supplementation.<sup>53</sup> A number of clinical studies and isolated case reports have reported abnormal dark adaptation in CF patients.<sup>54-57</sup> However, with modern supplementary management and appropriate intervention, the incidence appears to be infrequent.<sup>33, 58</sup> Once a regular complication,<sup>33,34,59</sup> the incidence of xerosis similarly appears to be uncommon or present only in patients with poor compliance.<sup>32,60</sup>

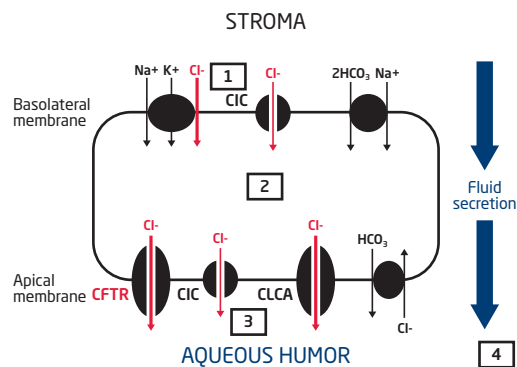


Figure 3 Diagram of a simplified corneal endothelial cell (1) Cl<sup>-</sup> enters the cell from the stroma via NKCC (Na<sup>+</sup>/K<sup>+</sup>/2Cl<sup>-</sup> co-transporter) and possibly ClC channels (voltage gated Cl<sup>-</sup> channels). (2) Intracellular Cl<sup>-</sup> levels are raised above equilibrium. (3) Cl<sup>-</sup> is secreted into the aqueous humor via CFTR, CLCA (calcium activated Cl<sup>-</sup> channels) and possibly ClC channels. (4) Fluid is secreted into the aqueous via osmosis

**The corneal endothelium**

The stroma has a natural tendency to swell; this is counteracted, primarily by the function of the corneal endothelium to maintain corneal transparency.<sup>48</sup> Fluid transport across the endothelium is secondary to the active transport of both Cl<sup>-</sup> and bicarbonate ions (HCO<sub>3</sub><sup>-</sup>).<sup>25</sup> This process is typically referred to as the 'endothelial pump'. It is presumed CFTR is involved in Cl<sup>-</sup> efflux from the endothelium and there-



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## Diabetic retinopathy

Cystic fibrosis-related diabetes (CFRD) is distinctly different from Type 1 and 2 diabetes mellitus, although it does share features of both forms.<sup>61</sup> The aetiology is not fully understood but proposed to be the result of decreased insulin secretion due to blockage of the pancreatic islet cells combined with increased insulin resistance as a result of the CFTR mutation and prolonged steroid use.<sup>62</sup> The prevalence of CFRD increases with age, at 30 years of age 50 per cent of CF patients are diabetic.<sup>63</sup> Unfortunately, there is little published literature regarding the prevalence of diabetic retinopathy (DR) in patients with CFRD. Occurrence appears to be high in those who have had CFRD for 10 years or more,<sup>64</sup> have poor glycaemic control<sup>65</sup> or poor compliance.<sup>66</sup> The high incidence of CFRD in adults and the knowledge that prevalence will increase with increased life expectancy highlights the need for regular eye examinations, with dilated examination of the fundus, in these patients.

## The crystalline lens

Posterior subcapsular cataract has been observed in CF patients (age range 5-20 years of age) receiving steroid treatment.<sup>67</sup> Steroid dose and duration were not predictive risk factors for lens opacification in this study however. Although no clinical evidence of lens opacity was detected by slit-lamp examination, lens transparency measured with a lens opacity meter has been found to be reduced in CF patients (age range 5-34 years of age).<sup>34,68</sup> It was suggested vitamin A deficiency could be a causative factor. Antioxidants, such as vitamin A, have received attention in their association with reduced cataract formation<sup>69</sup> and a number of studies have observed a reduced risk of lens opacity in those taking multivitamins which include vitamin A.<sup>70,71</sup> Diabetes is a well reported risk factor for cataract.<sup>72-74</sup> Therefore, a higher incidence of lens opacity could be expected in those with CFRD. As mean life expectancy continues to increase, the incidence of cataract in CF patients is likely to increase. Therefore, careful and thorough assessment of the crystalline lens should be included in the eye examination.

## The macula

The macular pigment is derived from two carotenoids, lutein and zeaxanthin which are derived solely from dietary ingestion.<sup>75</sup> Due to pancreatic insufficiency and subsequent deficient absorption, carotenoid concentrations

are typically low in patients with CF.<sup>76,77</sup> In a recent study, serum lutein and zeaxanthin concentration and macular pigment optical density were reduced in CF patients (21-47 years of age).<sup>78</sup> It has been suggested higher densities of macular pigment could function to protect against age-related macular degeneration (AMD).<sup>79</sup> As the survival rate of individuals with CF continues to increase it could be expected the incidence of atypically premature AMD in these individuals may also increase. As a consequence, the recommendation of a supplement containing lutein and zeaxanthin by a CF dietician to all CF patients may be pertinent.

## Contrast sensitivity

A reduction in contrast sensitivity (CS) has been observed in various studies of CF patients.<sup>80</sup> As CS had been shown to return to normal levels following vitamin A supplementation it was believed to be caused by subtle loss of photoreceptor function secondary to vitamin A deficiency.<sup>81</sup> However, abnormal CS has also been observed in vitamin A sufficient CF patients.<sup>33,58</sup> As CS is reduced in diabetes, even in the absence of DR,<sup>82</sup> CFRD may similarly affect CS. Cataract is also known to affect CS;<sup>83</sup> therefore the reduced lens transparency observed in CF patients may contribute. Therefore, practitioners should be

aware of the risk of reduced CS in these patients.

## Summary

It is apparent CF has numerous ocular complications. With breakthroughs in patient treatment, some, such as xerophthalmia, are now very uncommon. While dry eye appears to be a primary manifestation of CF, the causes of other complications, such as reduced CS, are unknown. Further improvements in life expectancy may see a large increase in the frequency of AMD, DR and cataract. Unfortunately many previous clinical studies are dated and have included confounding factors, such as CFRD or vitamin A status, or have been of a small scale. Therefore, detailed clinical studies of patients with CF are imperative so eye care practitioners can deliver optimal care to their patients. ●

## References

A full list of references is available at [opticianonline.net](http://opticianonline.net)

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## MULTIPLE-CHOICE QUESTIONS

**1** Which statement is correct?

- A CFTR has been observed in the corneal stroma
- B Dry eye is thought to be a primary manifestation of CF
- C CF is an autosomal dominant disease
- D CFTR regulates the flow of sodium ions

**2** Which process does CFTR not contribute to?

- A Regulation of the sub-retinal space
- B Basal tear production
- C Maintenance of corneal transparency
- D Aqueous humor production

**3** Which is a feature of Xerophthalmia?

- A Normal dark adaptation
- B Posterior subcapsular cataract
- C Conjunctival Xerosis
- D Blepharitis

**4** Which is not suggested as a cause of reduced contrast sensitivity in CF?

- A Reduced lens transparency
- B Vitamin A deficiency
- C Vitamin E deficiency
- D CFRD

**5** Which statement about CFRD is correct?

- A Prevalence is likely to increase as life expectancy rises
- B CFRD is the same as Type 1 diabetes mellitus
- C Diabetic retinopathy is uncommon in CFRD
- D CFRD is observed in 25 per cent of CF patients over 30 years of age

**6** Which has been observed in patients with CF?

- A Reduced inflammatory cytokine concentration in the tear film
- B Increased corneal thickness
- C Increased endothelial cell area
- D Increased macular pigment optical density

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