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Coexisting Cystic Fibrosis and Coloboma

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ABSTRACT

Cystic fibrosis (CF) is the most common genetic disorder in Caucasian individuals that primarily manifests asymptomatically in infants. As the disease progresses, CF patients present with multiple organ dysfunctions to include respiratory, gastrointestinal, and reproductive problems. Coloboma is an ocular defect resulting from incomplete or abnormal closure of the primitive embryonic fissure often co-occurs with congenital abnormalities and demonstrates varied genetic expression. The association of CF with coloboma has not been established in current literature. We report the case of a 27-year-old woman with a known history of CF and coloboma and her 21-month-old daughter that presented with both disorders similar to the mother. While CF and colobomas are traditionally regarded as unrelated conditions, this case highlights the potential connection between genetic mechanisms on chromosome 7 and developmental pathways involving the CFTR protein and coloboma-associated genes. Further research is warranted to explore this connection and inform future therapeutic strategies.

Keywords

Cystic fibrosis, Coloboma, CFTR mutation, Congenital disorder.

Introduction

Cystic fibrosis (CF) is caused by gene mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Specifically, there are over 2,000 CFTR variants and 700 disease-causing variants on chromosome 7, which are categorized based on their effects such as protein production and gating mutations [1]. In contrast, coloboma is an eye abnormality associated with congenital disorders that can present with mixed pleiotropic effects. Notably, several genetic inheritance patterns have been identified, and a few environmental causes have been linked to the development of colobomas [2]. Patient presentation can vary significantly due to colobomas appearing either in isolation or with other congenital malformations. Interestingly, various coloboma genes involved in ocular development have been implicated in the differentiation and activity of the CFTR protein.

Case Presentation

A 27-year-old woman (KS) with a known history of coloboma and CF-related pulmonary manifestations was evaluated for routine follow-up. Her past medical history is significant for asthma, pancreatic exocrine insufficiency, hypovitaminosis D, chronic rhinitis, and chronic sinusitis. Genetic testing confirmed CFTR mutations—3849+10kb C→T and Gly194X. Recent sputum cultures were positive for Pseudomonas aeruginosa and she has a history of colonization with this organism. The treatment regimen for KS included Cayston, Symdeko, Symbicort/levalbuterol, Bronchitol, Tobramycin, and daily chest physiotherapy with a vest. On physical exam, she weighed 94.6 lbs, with height of 59.5 inches, and BMI of 18.79. Vital signs were as follows—SpO_2 95% on room air (RA), temperature 96.6°F, heart rate 133 bpm, and respiratory rate 20/minute.

The 21-month-old daughter (AS) of KS was also present for evaluation. AS had been diagnosed with coloboma and CF via newborn screening, which revealed elevated immunoreactive

trypsinogen (IRT), two CF-causing mutations, and a positive sweat chloride test. Additionally, she had a history of upper respiratory infections, productive coughs, and pancreatic steatorrhea. Colonization with lung pathogens has been noted. On examination, her weight was 21.6 lbs (17th percentile), height of 31.5 inches (8th percentile), and BMI of 15.3 (35th percentile). Vital signs were SpO_2 99% on RA, temperature 97.3°F, heart rate 63 bpm, and respiratory rate 22/minute. Her treatment plan consisted of pancreatic enzyme replacement, Tobramycin, Pulmozyme, chest physiotherapy (CPT) daily, albuterol/budesonide, and daily AffloVest use.

Discussion

Coloboma: Genetic Component and Associated Syndromes

Eye development occurs in the developing fetus during the 5th-7th week of gestation. During this period, failure of ocular tissue to close can result in colobomas that affect various ocular components such as the ciliary body, iris, lens, retina, choroid, and optic nerve. Typically, colobomas present unilaterally, but they can also appear bilaterally asymmetrical [3].

Colobomas are associated with multiple congenital abnormalities, which can present either systemically or in isolation (non-syndromic). Systemic manifestations include pleiotropic effects such as cleft lip, microcephaly, and dysmorphic features. In particular, the CHARGE syndrome is commonly associated with colobomas and has featured anomalies such as heart defects, atresia choanae, retardation of growth, genital hypoplasia, and ear abnormalities [3]. Furthermore, colobomas can be associated with variable degrees of microphthalmos (small eye with structural abnormalities) and anophthalmia (absence of ocular tissue), creating a phenotype called the MAC spectrum [4]. Isolated colobomas can present in a dominant, recessive, or X-linked pattern. Most often, colobomas occur sporadically, making the precise inheritance pattern difficult to discern.

A wide array of genetic syndromes and inheritance patterns have been implicated: [3,4]

Autosomal Dominant:

- CHARGE syndrome
- Curry-Jones syndrome
- Renal coloboma (Papillorenal syndrome)

Autosomal Recessive:

- Aicardi syndrome
- Goltz focal dermal hypoplasia

X-Linked Dominant:

- Renpenning syndrome
- Lenz syndrome

Trisomy:

- Cat-eye syndrome (partial trisomy 22)
- Edward syndrome (trisomy 18)
- Patau syndrome (trisomy 13)

Deletions:

- Wolf-Hirschhorn syndrome
- Rubinstein-Taybi syndrome

Somatic Mosaicism:

- Oculocerebrocutaneous syndrome

The occurrence of coloboma with various syndromic conditions suggests that the process of optic fissure closure shares developmental pathways with other organ systems. For example, mutations in the paired box 2 (PAX2) transcription factor can result in congenital renal and ocular defects, such as papillorenal syndrome and optic nerve coloboma respectively [3]. Eye development requires several intrinsic transcription factors to interact and modulate extrinsic signals [3]. Intrinsic factors include PAX2, OTX2, and SOX2, while extrinsic factors include TGF, GDF3, GDF6, BMP4, and BMP7 [5]. Currently, 89 genes are associated with colobomas, each producing a different subset of phenotypic features [3,5-6].

Cystic Fibrosis: Genetic Component and Systemic Associations

CF is an autosomal recessive disease caused by mutations affecting the CFTR gene on chromosome 7. The most common CF mutation is the deletion of phenylalanine at position 508 (F508del). Less common CF-related variants can vary depending on the geographic region and ethnicity of the population. CFTR protein dysfunction leads to disrupted water-electrolyte balance which results in abnormally thick secretions across multiple organ systems. Affected systems include the upper and lower airways, pancreas, cervix, biliary tree, intestines, vas deferens, and sweat glands. Classic CF symptoms tend to be persistent respiratory infections, productive cough, elevated chloride sweat loss, and pancreatic insufficiency leading to the deficiency of both fat and fat-soluble vitamins [1].

Cystic Fibrosis and Coloboma

Current medical research does not show a relationship between CF and coloboma. However, genes involved in colobomas have been associated with the CFTR protein. There are four coloboma-associated genes on chromosome 7—ACTB, SHH, SEMA3E, SMO—that could potentially be affected by the CFTR gene variants and result in the MAC phenotype. The intrinsic and extrinsic factors involved in ocular development have been implicated in CFTR protein differentiation and function. Genetic factors such as RARB can modulate CFTR expression in proximal bronchial tubules [7], while alterations in CF ductal epithelial secretions implicate TGFβ, WNT, and BMP signaling [8]. FGFR1 and FGFR2 play roles in inflammatory lung disease and chaperone rescue of F508-CFTR protein [9]. FLNA regulates actin cytoskeleton reorganization, thereby enhancing CFTR membrane stability [10]. FOXA2 expression reduces mucus production in CF airways [11], and OTX2 maintains appropriate CFTR expression during airway epithelial differentiation through histone modification [12].

Conclusion

Existing literature does not establish a direct link between CF

and coloboma. However, the shared genetic loci on chromosome 7 and involvement of CFTR gene in ocular development suggest a potential connection. Both CF and coloboma have varied gene expressions and systemic manifestations, which demonstrate the complexity of understanding their underlying mechanisms. Further exploration of the molecular pathways involved in both conditions may provide valuable insights into their pathogenesis and potential therapeutic targets. This case presentation prompts continued investigation into the intersection of CF and ocular abnormalities to provide new insights for personalized treatment strategies and enhanced clinical management for affected individuals.

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