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Invited Article

A Historical Perspective of Cystic Fibrosis

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Abstract Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene which codes for a cyclic-AMP regulated chloride channel. Characteristic clinical features are recurrent pulmonary infections, exocrine pancreatic insufficiency and increased sweat electrolyte concentrations. CF was not clearly described in the medical literature until 1938. In this article the major discoveries and innovations that have been made since that time are reviewed and placed in historical context. They include the sweat test, comprehensive pulmonary and nutritional therapies, lung transplantation, discovery of the CFTR gene, and introduction of newborn screening. Therapies such as aerosolised mucolytic agents (dornase-α and hypertonic saline), aerosolised antibiotics (for example high-dose tobramycin and aztreonam) and CFTR modulator therapies such as ivacaftor have been developed in more recent years. These approaches have been associated with a significant increase in median life expectancy which reached 39.3 years in 2014.

Key words Cystic fibrosis; History of medicine

Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene which codes for a cyclic-AMP regulated chloride channel. The hallmark clinical manifestations are recurrent pulmonary infections, exocrine pancreatic insufficiency and increased concentrations of sodium and chloride in the sweat.[1] As a serious lethal disease of infancy, CF must have been present in the population, especially the Caucasian population where its incidence is highest, for millennia. It is therefore remarkable that the disease was only described clearly in the medical literature less than 100 years ago.[2] This article will summarise the progress that has been made since that time and the key milestones in the history of CF.

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Cystic Fibrosis in History

In 1857, Rochholz writing in an Almanac of Children's Songs and Games from Switzerland recorded that in German-Swiss folklore it was stated that "The child will soon die whose brow tastes salty when kissed".[3] This was one of the earliest recognitions of CF in modern times but the history of this observation is unclear. From the late 1800's until the 1930's there were isolated autopsy reports suggestive of CF and eventual recognition of what was termed the "Coeliac Affection" which incorporated both gluten sensitive enteropathy and CF. Several individuals such as Fanconi, Farber and others were well on the way to identifying CF by the late 1930's but the credit usually goes to Dorothy H Andersen, a pathologist working at Babies Hospital at the Columbia Presbyterian Medical Center in New York.

Dr Andersen was said to be a rugged individualist, a paediatric clinician, pathologist, and a research chemist - also apparently a roofer and carpenter, happy to make her own home improvements.[3] She is generally recognised as publishing the first clear detailed description of CF in 49 patients, describing the neonatal intestinal obstruction, intestinal and respiratory complications, and many other features - but particularly the characteristic pancreatic histology leading to the term fibrocystic disease of the pancreas. This seminal paper was published in 1938.[2]

In the 1940's Sydney Farber recognised CF as a generalised disorder, and introduced the term "mucoviscidosis."[4] The 2nd World War hindered medical research in general but military interests hastened the development of antibiotics such as penicillin. The median life expectancy in CF was only 18 months in the 1940's. The recessive mode of inheritance was recognised by Dr Andersen and colleagues at that time.[5]

In 1953, during a heat wave in New York City, Dr Paul di Sant' Agnese and colleagues identified the increased loss of salt in sweat of people with CF when several children were admitted to Columbia-Presbyterian with hyponatremic, hypochloremic alkalosis.[6] This eventually led to the development of the sweat test as a diagnostic test for CF. In 1955 CF research became national in the USA with the formation of the National CF Research Foundation; the first research grants were awarded to Drs. di Sant' Agnese, Andersen and Shwachman.[3]

Many new therapies were introduced at that time. Objective evidence of the beneficial effect of pancreatic enzyme therapy in children with CF was reported from Dr Norman's unit at Great Ormond Street, London, in 1955.[7] However, not all paediatricians were impressed with the effect of enzymes, maintaining that their unpleasant taste adversely affected the children's appetites.

Deficiencies of the fat soluble vitamins (A, D, E & K) were recognised as complications of severe steatorrhea, so vitamin supplementation was initiated. Shwachman mentioned that active physical therapy was instituted in his clinic in 1957 and he considered it to be one of the more important introductions into the treatment regimen with the goal of reducing the number of respiratory infections by removing mucus from the airways.[8]

The Sweat Test

During this period, the sweat test was introduced following the important observations by di Sant' Agnese and colleagues.[6] The initial methods involved heating the whole child and sweat was collected in a plastic bag or on weighed filter papers.[9] However whole body heating caused some cases of hyperthermia and at least one death.

Dr Paul di Sant' Agnese worked steadfastly to improve the sweat test as did others in the United Kingdom and North America. A method of inducing an area of sweating on the skin by pilocarpine iontophoresis was reported by Gibson and Cooke in 1959 and became the standard that is still used today.[10]

The 1960's

Much progress was made in the treatment of CF during the 1960's. By 1962, there was a burgeoning network of CF centers in North America and worldwide in other countries where CF was common such as Northern Europe, Australia and New Zealand. In 1962 the median life expectancy reached 10 years of age. In 1964, the North American CF Foundation (CFF) formed a basic science committee with the express intent of discovering the basic defect of CF and an effective cure for the disease.

In 1964 the group working at Case Western Reserve University in Cleveland reported that a standardised treatment regimen achieved better outcomes. It became known as the Cleveland Comprehensive Therapeutic Regimen and comprised: extra nutrition (increased calories and fat soluble vitamin supplements), airway clearance therapy, and aggressive use of antibiotics.[11] The approach was widely adopted and is given credit for the improved results that many centers started to report.

In the mid-1960's detailed patient registries were initiated in North America and Canada; subsequently many other countries and the EU developed similar registries which have been a rich source of epidemiological and outcomes data.[12-14] In recent years data from these registries have often served in place of phase 4, post-marketing studies of side-effects, for new drugs that have been licensed for CF.[15]

The 1970's

The 1970's were characterised by an ongoing intensive search for the basic defect of CF. Several serum factors were reported that impaired ciliary activity in culture and were thought to be possible causes of impaired mucociliary clearance in CF.[3] Several different methods for analysis of amniotic fluid were evaluated for prenatal diagnosis of CF

but none proved sufficiently reliable to guide prenatal genetic counseling.[16,17] By 1978 there were 100 accredited CF centers in the USA and many more worldwide.

The 1980's

The 1980's were a turning point for CF research. In 1981 Knowles and Boucher demonstrated an abnormally high potential difference across the nasal epithelium associated with increased sodium reabsorption and defective chloride secretion.[18] This discovery was followed within 2 years by the observation by Paul Quinton that there was a defect of chloride reabsorption in the sweat glands of people affected by CF.[19] This information, plus the results of later studies, paved the way for the eventual discovery that the mutation in CF affects CFTR, a chloride channel that also regulates sodium reabsorption by epithelia.[20-22]

Significant progress was also being made with clinical care. In 1985 the first heart-lung transplant for CF was performed in London, England, and other centers soon adopted the technique.[23] The first bilateral single-lung transplants were performed in Toronto in 1988.[24] This approach preserved the recipient's heart, which would recover its function rapidly once pulmonary hypertension was reversed, and reduced the need for cardiopulmonary bypass. It was a successful approach for end-stage lung disease that has since been adopted worldwide for many pulmonary diseases in addition to CF.

Newborn screening programs for CF were first developed and evaluated during the 1980's using a method based on measurement of immunoreactive trypsinogen in the blood spots collected on cards. Jeanette Crossley first described elevation of serum immunoreactive trypsinogen (IRT) concentrations in newborns with CF and the utility of Guthrie cards collected for the PKU test to measure IRT.[25] It was shown that most newborns with CF have persistently elevated values in the range 100-150 ng/ml. A randomised clinical trial of newborn screening for CF was began in Wisconsin, USA, in 1985 by Dr Phillip Farrell[26] and other trials were performed in the UK, Australia, Colorado and Massachusetts. Positive results from these trials led to a recommendation from a Consensus Committee formed by CFF and the CDC that newborn screening for CF was practicable and led to improved outcomes for nutrition and IQ.[27] This report and others were associated with rapid adoption of NBS in the USA, Canada, Europe, Australia, New Zealand and many other countries where CF is common.

New methods in genetic research led to an attempt to identify the gene for CF that was commenced in the mid-1980's by several competing research groups in North America and Europe. Initial linkage studies showed the gene was located on the long arm of chromosome 7.[28] An intensive genetic study was performed by a team of researchers from the University of Michigan and the University of Toronto and in 1989 they reported the identification, sequence and theoretical structure for a new gene that they termed the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene. The mutation that they recognised was Fdel508, the most common mutation, and the theoretical structure suggested that it was a cyclic-AMP regulated epithelial chloride channel.[20-22]

The 1990's

The discovery of the CF gene created many new opportunities that included: better understanding of the pathophysiology of CF, creation of a knock out mouse model, and targeted therapies such as gene therapy. It was quickly recognised that there were many more disease causing CFTR mutations and this discovery led to studies of genotype-phenotype correlations, and clinical diagnosis by mutation analysis.

Many important clinical innovations were introduced in the 1990's. This was time when national and international multicenter clinical trials became the standard for the efficient evaluation and licensing of new pharmacological agents. In 1994 the first mucolytic designed specifically for CF, dornase-α (Pulmozyme), was approved for marketing by Genentech and in 1997 the first aerosolised antibiotic developed specifically for CF, high dose tobramycin (Tobi), was approved by the FDA. Given the increasing number of agents available for clinical trials, a more streamlined, collaborative approach was needed and in 1998 the CFF initiated the Therapeutic Development Network (TDN).[29] This was an important development as many new therapies did become available in the ensuing years and their evaluation was facilitated considerably by the TDN.

The 2000's

The new millennium heralded many important developments. In 2000 the CFF initiated a drug discovery program for CF in partnership with a biotech company, Aurora.[30] The goal of this partnership was to discover new

pharmacological agents that would treat the CFTR defect and restore function to epithelial membranes, and the approach taken was to screen large libraries of compounds in assays that used cultured epithelial cells with a CFTR mutation. This approach was called "high throughput screening" and the number of compounds to be screened was so high that automated assays had to be developed that were capable of screening several thousand compounds per day for modulation of CFTR activity. Drugs that had this activity were classified into 2 types: CFTR *correctors* that would correct the synthesis and trafficking of CFTR in mutations such as delF508 and CFTR *potentiators* that would increase the activity of CFTR that was trafficked to the epithelium but that had reduced chloride channel gating activity. Within a few years there were candidate CFTR modulators in both categories that would go into clinical trials.

While this drug discovery initiative was in progress, other therapeutic approaches were discovered using established agents. In 2002 the first study was published that showed the benefit of long-term administration of the macrolide antibiotic azithromycin. The dose used was less than the usual antibiotic dose because the effect being sought was an anti-inflammatory effect and the results showed improvement in FEV1 and a reduction in the number of antibiotic courses required to treat infections.[31]

Then, in 2006, a study from Australia first reported the clinical benefits on pulmonary function of daily administration of hypertonic saline aerosols.[32] The theory was that hypertonic saline would normalise the composition and rheology of airway surface liquid leading to improved mucociliary clearance and pulmonary function. By 2008 the clinical care of CF had continued to improve to the extent that the median life expectancy in the CFF registry was around 38 years.

The following year saw the announcement of the first CFTR modulator by the Vertex Corporation which had acquired the intellectual rights to the drugs discovered in the CFF/Aurora program. The compound was called VX-770 and was shown in tissue culture to correct the CFTR activity of primary cultures of human bronchial epithelial cells that had one copy of the gating mutation G551D and a copy of Fdel508.[33] This compound moved quickly through phase 1 and phase 2 clinical trials. It was a small molecule that could be absorbed by the oral route and it appeared to have a good safety profile. A large phase 3 randomised, double-blind, placebo-controlled trial was completed in 2011 and demonstrated that VX-770 (now called ivacaftor) administration for 48 weeks was associated with significantly improved pulmonary function tests (FEV1), reduced respiratory symptoms, increased body weight, reduced risk of pulmonary exacerbations, and normalisation of sweat chloride values.[34] Since that landmark study, ivacaftor has also received approval from the FDA and other regulatory agencies for other gating mutations but unfortunately it was not effective as a single agent for patients homozygous for the Fdel508 mutation.[35] However in combination with the corrector VX-809 (lumacaftor), there was a small but significant improvement in pulmonary function and a reduction in the rate of pulmonary exacerbations when studied in homozygous Fdel508 patients with CF aged 12 years or more. The combination has been approved in the USA as Orkambi™.[36] Phase 3 trials of this combination are now in progress for such patients aged less than 12 years.

New correctors and potentiators are still in development by Vertex and by several other companies such as Novartis, Genzyme and Pfizer so it is likely that the first generation of CFTR modulators will eventually be replaced by more effective agents.[37]

Many other approaches are still in the therapeutic pipeline for CF. They fall into the categories of drugs that restore airway surface liquid, mucolytics, anti-inflammatory drugs, anti-infective agents, and nutritional support and these approaches are summarised in the CFF website.[37] While many new drugs hold promise for CF, it has also been shown that clinical outcomes can be improved significantly by consistent application of routine therapy and this has led to a focus on clinical quality improvement in CF;[38] it has been suggested that significant improvement in life expectancy could be achieved with consistent application of current treatments. In 2014, the median life expectancy in people with CF was 39.3 years (95 percent confidence interval: 37.3-41.4 years) and for those with intact pancreatic function it is much greater. While there is still much more work to be done, analysis of registry data suggests that the survival rates will continue to increase, even before taking the outcomes of newborn screening, and the availability of CFTR modulator drugs into consideration.[39]

In this article I have provided a historical perspective of CF from the time of its first recognition until the present. Remarkable progress has been made over the last 75 years and I am confident that the progress will continue at a high rate given all the potential therapies that are in clinical trials and the commitment that society has made to find in an effective cure for this severe genetic disease of young people.

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Declaration of Interest

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