

Diving into Cystic Fibrosis History: Major Milestones

Maria Moreno Ortega*, **Macarena Queralt García de Góngora** and **Isabel Delgado Pecellín**

Paediatrician at the Children's Hospital of the Virgen del Rocío University Hospital, Seville, Spain

***Corresponding Author:** Maria Moreno Ortega, Paediatrician at the Children's Hospital of the Virgen del Rocío University Hospital, Seville, Spain.

Received: June 17, 2021; **Published:** July 29, 2021

"Knowing the history of a disease indicates the way to reduce or eradicate it"

Marvin J Allison.

Cystic fibrosis (CF, OMIM # 219700, ICD-10 # E84) is a chronic, multisystemic disease, which classic clinical manifestations are respiratory infections, pancreatic insufficiency and increased sweat chloride concentration [1,2].

There are historical references related to these clinical manifestations for centuries before their description as a disease. As a first mention, the following 15th-century Irish saying would be translated: "Woe to that child who, when kissed on the forehead, tastes salty. He is bewitched and will soon die" [1,3,4]. In 1606, Juan Alonso y de los Ruyzes de Fontecha, professor of Medicine at the University of Alcalá de Henares, wrote in their book "Ten privileges for pregnant women" [5]: "...he says he knows to bewitched people if when scratching their foreheads, you later once a salty taste on your fingers...".

If we examine bibliographic sources, we will find these and other similar ancient stories in numerous towns of European countries (Poland, Russia, Hungary, Czechoslovakia, Italy, or Switzerland), in which classic symptoms of the disease are related to witchcraft, bewitchment, or "evil of eye"; as circumstances associated with early death [3].

But we do not find evidence of the existence of the disease only in traditional elements of European folklore, but also in other spheres. Peter Paaw, professor of Botany and Anatomy at the University of Leiden, carried out an autopsy in 1595 on an 11-year-old patient - whom they believed to be haunted - who had presented malnutrition and "septic fever" [6]. We could be referring to the first pathological description of the disease; which details an enlarged and shiny pancreas, with a "cirrhotic" aspect, they said. In subsequent years, autopsies of patients with similar symptoms - most of them paediatric - are reported, whose common denominator is the presence of a diseased pancreas (Georg Seger, 1673; Gerardus Leonardus Blasius, 1677) [6]. In the 18th century, the Swedish Nils Rosen von Rosenstein - considered one of the fathers of paediatrics - describes a disease, *fluxus coeliacus*, which causes diarrhea, growth retardation, weakness, and hardening of the pancreas (De Morbis Infantum, 1752) [6]. In the 19th century, the Austrian Carl Von Rokitansky¹ described what was probably a meconium ileus after performing a fetal autopsy in which he found an intestinal perforation and meconium in the peritoneal cavity. If I may be curious about an event of this century, I will mention the mystery about the death of the Polish composer Frédéric Chopin, the cause of which has been discussed in multiple publications during subsequent years [7,8]. Among the indications that point to cystic fibrosis as an underlying disease stand out among other data: the affection shared with two of his sisters (one of them, Emilia, who

¹Austrian medical pathologist, humanist and philosopher, known among other things for introducing the concept of ethics applied to medicine, having contributed to the description of the Rokitansky-Küster-Hausner syndrome and having developed the "Rokitansky Technique", an autopsy method which is still in effect today.

died at the age of 14), the cough of years of evolution with recurrent pulmonary infections, episodes of haemoptysis, significant malnutrition or the description in his autopsy of an enlarged heart, which could be related to core pulmonale, a complication of advanced lung disease [9,10].

But the twentieth century is undoubtedly the century in which the knowledge of the disease is developed in-depth. In 1905, Karl Landsteiner² described the association between thick meconium in new-borns and pancreatic fibrosis, posing an enzyme defect as the cause [11].

In 1936, the paediatrician Guido Fanconi characteristically related pancreatic involvement and pulmonary disease [12]; although the term cystic fibrosis (of the pancreas) was not coined until 1938, when the pathologist Dorothy H. Andersen (USA, 1901-1963) described the symptoms of the disease and the histology of the pancreas, distinguishing it from other diseases with similar symptoms such as celiac disease [13]. In the same year, Kenneth Blackfan and Charles May described 35 paediatric patients with fibrosis-pancreatic atrophy and dilation of ducts and acini due to “high viscosity” secretions [14].

In 1943, Sydney Farber - known for his important contribution to paediatric oncology - raised cystic fibrosis as a systemic disease, coining the term “*mucoviscidosis*” [15].

Dorothy H. Andersen herself inferred in 1946 the genetic nature of the disease, proposing an autosomal recessive inheritance [16]. In this same year, she used, together with Paul Di Sant’Agnese³, penicillin (especially inhaled) and sulpha drugs for the treatment of repetitive respiratory infections in these patients [17]; despite the “age of antibiotics” had started years before a her the discovery of penicillin by Alexander Fleming (Lochfield, Scotland, United Kingdom) in 1928. After a New York heatwave (1953), Di Sant’Agnese related an excessive loss of salt in the sweat of CF patients [18], a clinical observation that promoted the subsequent development of the classic test for the diagnosis of the disease or “sweat test”, based on the iontophoresis method with pilocarpine devised by L. E. Gibson and R. E. Cooke [19]; which is considered today the gold standard for the diagnosis of the disease.

The following decade is characterized by the development of associations and specific centres for the study and management of the disease; emerging in this context encouraging strategies for the treatment of recurrent pulmonary infections [20], respiratory physiotherapy programs [21], or new alternatives in the nutritional approach of these patients. In this regard, mention should be made of the Canadian Douglas N. Crozier of the Hospital for Sick Children in Toronto, who - breaking with tradition - proposed a diet rich in fat and supplementation with high-dose pancreatic enzymes, substantially modifying the nutritional criteria applied up to that moment [22].

However, in the 70s, despite the aforementioned advances, the life expectancy of affected patients continued to be significantly reduced, since most died in childhood or adolescence after years of suffering, and survival in adulthood was exceptional.

Important progress took place in the 1980s. Thus, in 1981, the pulmonologist Michael Knowles demonstrated the abnormally high potential difference in the nasal mucosa [23], which would reflect the existence of an alteration in the epithelial function. Based on this, Paul Quinton, a physician at the University of California and at the same time affected by CF, takes a decisive step in the understanding of the basic defect of the disease in 1983 by publishing that there is an impermeability to chlorine in sweat glands; which, transferred to

²Austrian professor in pathological anatomy, known for having performed blood group typing, work for which he was awarded the 1930 Nobel Prize in Medicine and Physiology.

³Key scientist in the knowledge of cystic fibrosis and founder of the American cystic Fibrosis Foundation; who postulated the existence of abnormal sweating in CF patients.

other epithelia, would explain the increased viscosity of the secretions of these patients [24]. On the other hand, in 1985 the CFTR [25,26] gene was mapped, discovering four years later the most frequent mutation called $\Delta F508$ [27].

Neonatal screening programs also deserve to be mentioned, due to their interest and impact on the prognosis of CF; promoted by the New Zealander Heanney Crossley, who used a drop of dried blood for the detection by immunoassay of abnormally high amounts of trypsin in these patients [28,29]. Simultaneously, over the years, strategies have been developed to control respiratory infections (especially against the microorganism *Pseudomonas aeruginosa*) that include the administration of parenteral antibiotic therapy [30] and nebulized therapy [31].

Another spectacular advance of this decade was the performance of heart and lung transplants in patients in advanced stages, which achieved successful survival rates of over 70% at two years [32]. Favorable results were also obtained for liver transplantation in patients with CF and severe liver disease [33].

In 1990, an article was published in the prestigious *Nature* after managing to correct for the first time the defect of the chloride channels of epithelial cells employing CFTR expression (not mutated), demonstrating a causal relationship between CFTR gene mutations and defective transport chloride [33], the hallmark of the disease. Three years later, at the University of Oxford, the correction of conductance defects in the trachea of transgenic mice would be achieved through the use of liposomes for gene transfer [34]. Soon after, the first attempt of this type of treatment using adenovirus as a vector through the nasal mucosa of patients would be published [35]. These facts would open the door to gene therapy in humans with cystic fibrosis. In the clinical sphere, the implementation of new therapies will stand out over those years. Therefore, we obtained new inhaled therapies, such as DNase [36] or tobramycin [37] and oral therapies, such as the new commercial preparations of pancreatic enzymes with high doses of lipase [38]-which allowed reducing the number of capsules to be ingested-, or azithromycin in patients with chronic infection of *Pseudomonas aeruginosa* [39]. Another subsequent initiative was the use of inhaled hypertonic saline solutions, with satisfactory results concerning the mucociliary clearance of secretions.

The 21st century could be considered the century of the beginning of personalized Medicine. Cystic fibrosis patients are excellent candidates to use this Medicine since its genetics and pathophysiology are widely known nowadays and specific therapeutic targets have been identified. Regarding gene therapy, animal models have been developed [40,41] to implement the proposals started in the 90s. Besides, recombinant vectors, both viral and nanoparticles, with therapeutic DNA have been used having as an objective the insertion of this DNA into cell targets [42]. The current reality is a therapy aimed at restoring the function of the protein, there are CFTR corrective and enhancement drugs whose target is in effect the CFTR protein; achieving, respectively, the correction of the protein transport to the cell membrane or improving its function once it is located there [43-46].

Technological advances and the Careless effort of the scientific community have favoured us to amend a quantitative and qualitative leap in terms of knowledge of the disease, which has resulted in an exhaustive approach to the patient from a multidisciplinary perspective. Consequently, initiatives such as presymptomatic diagnosis thanks to the implementation of neonatal screening strategies, greater access to repair drugs and therapies for the control of chronic bronchial infection, progress in the nutritional approach, and improved results in lung transplantation have made cystic fibrosis go from being a little-known and frequently fatal genetic disorder a hundred years ago in infants and children to currently become a complex multisystemic entity that affects children and adults, progresses significantly in quality of life and survival and constitutes the working engine of a wide range of specialists worldwide.

Bibliography

1. Salcedo A., *et al.* "Tratado de Fibrosis Quística (2012): 551.
2. Mall J. "Stuart MAE, editor: Cystic Fibrosis". *European Respiratory Society* (2014): 332.

3. Navarro S. "Recopilación histórica de la fibrosis quística". *Journal of Gastroenterology and Hepatology* 39.1 (2016): 36-42.
4. Astudillo P. "Historia de la fibrosis quística (2020).
5. Diez privilegios para mugeres preñadas. Con un diccionario medico - Juan-Alonso de Fontecha - Google Libros (2020).
6. Busch R. "On the history of cystic fibrosis. Acta Universitatis Carolinae". *Medica* 36 (1990): 13-15.
7. Cheng TO. "Chopin's illness". *Chest* 114.2 (1998): 654.
8. Wiy M., et al. "A Closer Look at Frederic Chopin's Cause of Death". *American Journal of Medicine* 131 (2018): 211-212.
9. Majka L., et al. "Cystic fibrosis - A probable cause of Frédéric Chopin's suffering and death". *Journal of Applied Genetics* 44 (2003): 77-84.
10. O'Shea JG. "Was Frédéric Chopin's illness actually cystic fibrosis?" *Medical Journal of Australia* 147.11-12 (2020): 586-589.
11. Landsteiner K. "Darmverschluss durch eingeductes meconium pankreatitis". *Zentralblatt für allgemeine Pathologie* 16 (1905): 903-907.
12. Fanconi G., et al. "Das Coeliakie-syndrom bei angeborener zysKscher Pankreasfibromatose und Bronchiektasien". *Wiener Medizinische Wochenschrift* (1936).
13. DH A. "Cystic fibrosis of the pancreas and its relation to celiac disease: A clinical and pathologic study". *The American Journal of Diseases of Children* (1938).
14. Blackfan KD and May CD. "Inspissation of secretion, dilatation of the ducts and acini, atrophy and fibrosis of the pancreas in infants. A clinical note". *The Journal of Pediatrics* (1938).
15. Farber S., et al. "Pancreatic Enzyme Activity and the Celiac Syndrome". *Journal of Clinical Investigation* 22.6 (1943): 827-838.
16. Andersen DH and Hodges RG. "Celiac syndrome; genetics of cystic fibrosis of the pancreas, with a consideration of etiology". *The American Journal of Diseases of Children* (1946).
17. Di Sant'agnese PEA and Andersen DH. "Celiac syndrome; chemotherapy in infections of the respiratory tract associated with cystic fibrosis of the pancreas; observations with penicillin and drugs of the sulfonamide group, with special reference to penicillin aerosol". *The American Journal of Diseases of Children* (1946).
18. DI Sant'agnese PA., et al. "Abnormal electrolyte composition of sweat in cystic fibrosis of the pancreas; clinical significance and relationship to the disease". *Pediatrics* (1953).
19. Gibson LE and Cooke RE. "A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis". *Pediatrics* (1959).
20. Mayhews LRW., et al. "A therapeutic regimen for patients with cystic fibrosis". *The Journal of Pediatrics* (1964).
21. Doyle B. "Physical therapy in the treatment of cystic fibrosis. - PubMed – NCBI". *Physical Therapy Reviews* 39.1 (1959): 24-27.
22. Crozier DN. "Cystic fibrosis. A not so fatal disease". *Pediatric Clinics of North America* (1974).
23. Knowles M., et al. "Increased Bioelectric Potential Difference across Respiratory Epithelia in Cystic Fibrosis". *The New England Journal of Medicine* 305.25 (1981): 1489-1495.

24. Quinton PM. "Chloride impermeability in cystic fibrosis". *Nature* (1983).
25. Tsui LC, et al. "Cystic fibrosis locus defined by a genetically linked polymorphic DNA marker". *Science* 80 (1985).
26. Wainwright BJ, et al. "Localization of cystic fibrosis locus to human chromosome 7cen-q22". *Nature* 318.6044 (1985): 384-385.
27. Rommens JM, et al. "Identification of the cystic fibrosis gene: Chromosome walking and jumping". *Science* 80 (1989).
28. Crossle JR, et al. "Dried-Blood Spot Screening For Cystic Fibrosis In The Newborn". *Lancet* 313.8114 (1979): 472-474.
29. Wilcken B, et al. "Cystic fibrosis screening by dried blood spot trypsin assay: Results in 75,000 newborn infants". *The Journal of Pediatrics* 102.3 (1983): 383-387.
30. Gilbert J, et al. "Home intravenous antibiotic treatment in cystic fibrosis". *Archives of Disease in Childhood* (1988).
31. Hodson ME, et al. "Aerosol Carbenicillin And Gentamicin Treatment Of Pseudomonas Aeruginosa Infection In Patients With Cystic Fibrosis". *Lancet* (1981).
32. Yacoub MH, et al. "Heart-lung transplantation for cystic fibrosis and subsequent domino heart transplantation". *The Journal of Heart and Lung Transplantation* (1990).
33. Miele LA, et al. "Liver transplantation in cystic fibrosis". *Lancet* 1.8646 (1989): 1073.
34. Hyde SC, et al. "Correction of the ion transport defect in cystic fibrosis transgenic mice by gene therapy". *Nature* (1993).
35. Zabner J, et al. "Adenovirus-mediated gene transfer transiently corrects the chloride transport defect in nasal epithelia of patients with cystic fibrosis". *Cell* (1993).
36. Fuchs HJ, et al. "Effect of aerosolized recombinant human dnase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis". *The New England Journal of Medicine* (1994).
37. Ramsey BW, et al. "Intermittent administration of inhaled tobramycin in patients with cystic fibrosis". *The New England Journal of Medicine* (1999).
38. Taylor CJ and Dodge JA. "High-strength pancreatic enzyme supplements and large-bowel stricture in cystic fibrosis". *Lancet* (1994).
39. Saiman L, et al. "Azithromycin in Patients with Cystic Fibrosis Chronically Infected with Pseudomonas aeruginosa: A Randomized Controlled Trial". *The Journal of the American Medical Association* (2003).
40. Rogers CS, et al. "Disruption of the CFTR gene produces a model of cystic fibrosis in newborn pigs". *Science* (2008).
41. Sun X, et al. "Disease phenotype of a ferret CFTR-knockout model of cystic fibrosis". *Journal of Clinical Investigation* (2010).
42. Derichs N. "Targeting a genetic defect: Cystic fibrosis transmembrane conductance regulator modulators in cystic fibrosis". *European Respiratory Review* (2013).
43. Boyle MP and De Boeck K. "A new era in the treatment of cystic fibrosis: Correction of the underlying CFTR defect". *The Lancet Respiratory Medicine* (2013).
44. Castellani C, et al. "Benchmarks for Cystic Fibrosis carrier screening: A European consensus document". *Journal of Cystic Fibrosis* 9 (2010): 165-178.

45. Flume PA, *et al.* "Ivacaohor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation". *Chest* (2012).
46. Chaudary N. "Triplet CFTR modulators: Future prospects for treatment of cystic fibrosis". *Therapeutics and Clinical Risk Management* (2018).

Volume 10 Issue 8 August 2021

©All rights reserved by Maria Moreno Ortega, *et al.*