Imaging Cystic Fibrosis: A Case Study

Abstract

Medical imaging provides an invaluable service for the diagnosis and treatment of cystic fibrosis. A wide array of modalities including radiology, CT, MRI, and ultrasound all contribute to possible diagnosis. Each modality is valuable in detecting different symptoms that can arise due to cystic fibrosis. Possible connections between abdominal and pulmonary pathologies have increased the likelihood of catching cystic fibrosis using multiple imaging modalities together. Although the research of cystic fibrosis is still on a small scale, new drugs are starting to show promising results in relinquishing the effects of cystic fibrosis quickly and effectively.

Introduction

Every year, about 1 000 new cases of cystic fibrosis (CF) are diagnosed. About 30 000 people in the US and over 70 000 people worldwide have already been diagnosed with CF.¹ Of these cases, 70% were diagnosed before the age of two. Of those, only 45% diagnosed are currently over 18 years old. The predicted average age of those diagnosed is into their late 30s.¹ This is extremely lower than the average age of HIV/AIDS’ life expectancy into their 70s.² Yet there is a monstrous amount of money put into research for these diseases while CF research is still in its infancy. Perhaps this has to do with the lack of public awareness when it comes to CF.

CF is a fairly uncommon disease that requires the appearance of deltaF508 and p.R347L mutations of the cystic fibrosis transmembrane receptor (CFTR) on different chromosomes in order to manifest itself in the human body.³ CF is an autosomal recessive disease that can affect later generations of offspring. It is most commonly diagnosed in early childhood after symptoms of pulmonary difficulties. CF is also a degenerative disease that affects the lungs and digestive system of those diagnosed. It causes the patient’s lungs to be filled with thick and sticky mucus. It also affects the pancreas creating the abnormal function of an enzyme responsible for digestion and absorption.¹ Although these symptoms are not directly life threatening, they open pathways for infection and degeneration in the lungs and intestines. Due to the mucus buildup in the lungs, persistent coughing and wheezing can cause a shortness of breath. The fluid buildup can also lead to bronchiectasis.
In the intestines, the lack of absorption of nutrients can cause weight loss and body weakness. A byproduct of insufficient absorption can be painful bowel movements due to harder stool backed up in the intestines.¹ The result is a very uncomfortable life for those with CF. The lack of lung function limits the type and length of physical activities patients can participate in. Insufficient nutrients take away energy and total body health. The improvement of CF healthcare is a necessity and medical imaging is at the front line of diagnosis and treatment.

Medical Imaging Leads the Way

CF is the most common life-limiting genetic disorder in the white population, with 1 diagnosis every 3,200 newborns in the United States.⁴ The use of X-rays has increased since its discovery in 1895. Medical imaging has evolved from conventional X-rays to various modalities, each more complex than the previous. The different modalities of medical imaging all provide a different form of diagnosis for CF. Radiology, Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Ultrasound all provide valuable information relevant to patient diagnosis. These modalities also help monitor the disease to help healthcare providers make more educated decisions about how to treat each individual patient. Although there is no cure for CF, the use of medical imaging can help to monitor and control the disease. The goal is to increase patient comfort as well as life expectancy. Each modality plays its own role in the healthcare process.

Radiology

X-rays are the most conventional, as well as the most used, imaging modality in healthcare. They are also most commonly used for the diagnosis of CF. X-rays are used to screen the lungs of patients either thought to have CF or those already diagnosed. One of the most severe effects of CF is the infiltration of heavy, sticky fluid buildup in the lungs. This change in density inside lung tissue can be easily seen on a chest X-ray. Radiologists look for the plugging of small bronchioles which results in the hyperinflation of the lungs. Nodules on the radiograph are interpreted as mucus buildup inside the lungs. Diagnostic clues such as tram-trackings highlight the presence of pulmonary pathology. Tram-tracking is the parallel linear densities that stand out from their surrounding tissues.⁵ Patients with CF often have tram-track signs in the
upper lobes of the lungs, which branch out from the main bronchi. These tram-tracks are the thickening of the bronchial walls that don’t appear in healthy patients (see Figure 1).

Routine chest radiographs of patients diagnosed with CF are scheduled every 2-4 years to monitor any progressions. Patients with serious or frequent pulmonary complications are seen annually to stay on top of more severe effects. Complications often seen on CF chest radiographs include:

- Bronchiectasis.
- Hyperinflation.
- Bronchial thickening and dilatation.
- Peribronchial cuffing.
- Mucoid impaction.
- Cystic radiolucencies.

The downside to conventional chest radiography is the lack of definition in the images provided. However, chest radiographs are low dose and still a good way to diagnosis CF. It also provides a baseline image for the condition of the lungs. This allows physicians to monitor the disease as well as make early decisions of treatment options. For more specific and detailed images, other modalities should be utilized. Although radiographs remain useful for baseline studies, they are being supplemented or replaced by state-of-the-art techniques, such as High Resolution Computed Tomography (HRCT) scans and Positron Emission Tomography (PET) scans.

Composed Tomography

Over the past 20 years, the development of the Bhalla scoring system has provided a consistent baseline for grading pulmonary degeneration. This scoring system incorporates plain chest radiographs with CT scans to provide patients with a Bhalla Score. These scores are used to predict the probability of pulmonary disease over time. The Bhalla Score became the most commonly used pulmonary grading system. However there were flaws in the consistency and accuracy of the Bhalla Score when studying patients with CF. Once the importance of these scores was identified, physicians started the development of a more consistent scoring system.

Brody and his colleagues began to grade structural damage of the lungs, most notably bronchiectasis, using chest CTs (see Figure 2). They revised the scoring system to better
represent pulmonary degeneration in patients with CF. Now the most common pulmonary grading system used is the Brody scoring system. In a new study, Saunders, using the new Brody scoring system, was able to show a significant association between the baseline severity of lung disease and the subsequent scores obtained from the same study done 7.5 years later. The scores correctly predicted not only future lung function but also future Brody scores.

One of the most interesting findings in the study done by Saunders is that the chest radiograph scores were not out-performed by the CT scores in terms of predictability. This begins to bring into question the necessity of CT scans in improving predictability of lung disease. Patients with CF are prone to yearly radiation exposure to monitor the progression of their disease. If CT scans provide no advantages in diagnosing pulmonary degeneration, one could see the continuous monitoring of these diseases move towards the plain chest radiograph due to substantially less radiation exposure to the patient.

The average age for introduction to the Saunders’ study was 11.5 years old. This initial study becomes the baseline for the patient’s future testing. The earlier the baseline study is performed, the faster a diagnosis can be made. Healthcare cannot undersell the importance of the CT scan in evaluating CF. However for at risk children, it may be in their better interest to rely on plain chest radiographs to provide diagnostic images. Using the data from Saunders’ study, it is possible to maintain diagnostic quality while still being conscious of patient safety from radiation exposure. While the Brody score has been a substantial step for pulmonary diseases monitoring, it will still require both chest radiographs and CT scans in order to find any direct connection between early diagnostic findings and future pulmonary outcomes.

**Magnetic Resonance Imaging**

In conjunction with pulmonary degeneration, pancreatic atrophy can also be a possible sign of CF in adults. Pancreatic atrophy is most commonly found in elderly patients. Therefore a young adult that shows the same symptoms are sometimes suspected to have CF. Adults rarely show the same pulmonary difficulties that children show as signs of CF. Therefore it is much harder to diagnose CF in young adults. However due to recent studies of the pancreas and with the aid of MRI, scientists think they may have found a connection.

Young adults more commonly show symptoms of gastrointestinal problems rather than pulmonary issues. Of these gastrointestinal problems, complications in the pancreas are the most
prolific. Due to this, diagnosticians have begun to connect pancreatic atrophy to CF (see Figure 3). However this connection alone is not enough for a diagnosis. In the event that a patient has gastrointestinal problems and pancreatic atrophy is found on the subsequent MRI, the next step is to obtain genetic counseling to look for the deltaF508 and p.R347L gene mutations that are responsible for CF. According to Stratton et al., \(^3\) “to date there are less than 10 published cases of initial diagnosis of CF secondary to pancreatic dysfunction”. \(^{(p.151)}\) The use of MRI and pancreatic atrophy to diagnose CF is primarily used for young adults. Most patients diagnosed with CF are done so in early childhood due to pulmonary difficulties. This is why there are so few pancreatic dysfunction aided cases of diagnosing CF.

Although the research is still early, there is a positive outlook for the usefulness of MRI in diagnosing CF. Not only is MRI the primary modality for finding pancreatic deformities, it is also one of only two modalities that exposes the patient to zero radiation. X-ray and CT are still the primary modalities that allow CF patients to be diagnosed and treated for their condition. A full-proof diagnosis for young adults has yet to be found. However, with the aid of MRI and its connection to pancreatic atrophy, CF diagnosis in young adults is still plausible. \(^3\)

**Sonography**

Secondary to pulmonary disease, liver complications are the most common cause of death of those with CF.\(^10\) When using ultrasound, the lining of the liver can be scanned, showing coarse and nodular marks identifying cirrhosis. Liver manifestations secondary to CF start in the biliary ducts.\(^11\) CF causes all fluids in the body to thicken such as the mucus that floods the lungs. The same thickening happens to the bile running through the biliary system, causing clogs and cytotoxic damage. This damage leads to periportal fibrosis, bridge fibrosis, and focal biliary cirrhosis.\(^12\) The spleen can be inflamed, a common sign of splenomegaly developed due to portal hypertension.

Another common organ scanned with ultrasound is the pancreas and associated biliary ducts. Pancreatic manifestations are seen in nearly 90% of all CF cases.\(^12\) Vessels and ducts can be measured to look for dilation, strictures, or obstructions (see Figure 4). An example is a case in which a 36 year old male that was diagnosed with CF had an abdominal ultrasound to monitor his biliary tract.\(^11\) A scan of his gallbladder showed a decrease in gallbladder size and an increase in the thickness of the walls and the calculus in the lumen. Liver manifestations usually follow
CF. These side effects include the thickening of bile and cytotoxic damage to the biliary ducts. This can obstruct the collection of bile in the gallbladder.\textsuperscript{11} The discovery of these occurrences lead to further investigation into secondary pathology. CF can be diagnosed by association with these secondary diseases. However visualization of the gallbladder and the biliary ducts through ultrasound can be difficult on patients with CF.

Following numerous studies, Biglin et al\textsuperscript{11} found ultrasound to be a useful screening technique to visualize hepatobiliary changes in patients with CF. Ultrasound has its limitations in diagnosing CF. However the upside is the exclusion of radiation in order to obtain diagnostic images. Ultrasound is most commonly used to size and measure anatomy. It also has the ability to show function in real time. This gives physicians the ability to determine functional information about how the body is working. This is important for CF patients due to the possible obstruction of the biliary system.

**CF Radiation Dose**

The use of medical imaging has been increasing every year since the discovery of its diagnostic qualities. This unfortunately leads to an increase in cumulative effective dose (CED), or the amount of radiation received by the patient. Terminally ill patients, such as those with CF, undergo dozens of diagnostic procedures. Their CED is much higher than the average patient per year. This extremely high amount of radiation brings with it the increase in possible cancerous malignancies. In a study done by O’Connell and his associates\textsuperscript{13}, the amount of radiation received by CF patients due to radiation exposure was calculated and analyzed per radiographic procedure.

In the first part of the study 5 596 patients with CF, ranging from infants to adults were monitored during typical imaging procedures. During a plain chest X-ray and a CT abdomen, the CED increased as the patient got older. The only 2 that decreased with age were CT pulmonary angiograms and barium swallows.\textsuperscript{13} The data can be useful in helping the ordering physicians decide which procedure to order (see Table 1). This means there could be the possibility of using a lower CED procedure based on the age of the patient to achieve the same diagnostic images.

Continuing their study, O’Connell et al\textsuperscript{13} recorded the type of procedures performed on the CF patients and compared 3 different study periods. Compiling information from all 3 studies, 5 596 radiologic procedures were performed: 4 730 were general radiographs, 406
ultrasonographies, 241 CT scans, 127 interventional procedures, 74 fluoroscopies and 18 nuclear medicine procedures. A graph was created (see Figure 5) to illustrate the connection between total number of procedures performed and the percent of CED to the patient from those procedures. Radiographs accounted for 74% of the procedures performed, but only 6% of the total CED; while CT accounted for only 8% of the procedures performed, but 74.8% of the CED.

This information supports the position that plain film radiography provides the best care for CF patients. However, with this data, ordering physicians can decide whether or not the exposure is warranted. The Image Wisely campaign for adults and the Image Gently campaign for children were created to decrease patient radiation exposure. The first step to being able to effectively decreased CED is to increase understanding about which procedures deliver the highest CED.

**Case Report**

CF causes a mutation in the gene that controls the chloride transport system in the exocrine system. Without proper function, thick fluid build-up begins to occur. The thick mucus allows for bacteria such as staphylococcus aureus and pseudomonas aeruginosa to multiply. Patients rarely die because of the fluid infiltrating their lungs. The leading cause of death for patients with CF is the subsequent infection, decreasing lung function, causing respiratory insufficiently. Experimental treatments are beginning to focus on decreasing the amount of fluid build-up in the lungs; thus decreasing infection rates. In a study done by Sermet-Gaudelus, Ivacaftor was approved as a style of personalized medicine for the treatment of CF patients over 6 years old. Ivacaftor is only for treatment of patients with the specific CFTR mutation, G551D.

In phase I of the study, Sermet-Gaudelus identified Ivacaftor as being able to specifically target the G551D gate mutation. The effect increases the probability that the gate mutation will open at the cell surface. This allows for ions to pass through the cell membrane, restoring more normal fluid transportation in the body. To begin phase II of the study, 12 CF patients with at least 1 of the mutated G551D were selected. Half of the patients were randomly selected to receive Ivacaftor every 12 hours at controlled doses, while the other half received a placebo. The Ivacaftor was tolerated very well by the patients with adverse effects including:
nausea, fevers, and coughs. Most importantly, Ivacaftor showed an improvement of ion transfer between cells in both nasal and sweat glands. This was this first study of CF patients with normalization of sweat chloride levels.\textsuperscript{14} Lung function also showed levels of improvement after the administration of Ivacaftor. These findings garnered further investigation into the usefulness of Ivacaftor as a target therapy for CF patients with the G551D mutation.

In phase III of Sermet-Gaudelus\textsuperscript{14} study, the effectiveness and safety of Ivacaftor between children and adults was determined. After the 48 week double-blind study was completed, the results were inspiring. Significant improvement of lung function was seen due to the Ivacaftor therapy. As seen in Figure 6, after 24 weeks there was a significant statistical treatment effect of 10.6\% points for adults taking Ivacaftor. In the same 24 weeks, there was a -0.2\% point drop for patients taking the placebo. The most significant finding was the swift improvement shown after just 15 days taking Ivacaftor. In the same study done with pediatric patients, data showed a 12.5\% point increase after 24 weeks on Ivacaftor.\textsuperscript{14}

The rate of pulmonary exacerbations also saw a decrease. After 48 weeks, 67\% of the patients taking Ivacaftor were free of pulmonary exacerbations versus just 41\% of the placebo patients (see Figure 7).\textsuperscript{14} The decrease in pulmonary exacerbations is due to the effect Ivacaftor has on chloride transport function. In another part of the study, sweat chloride concentrations were monitored. In some patients, the sweat chloride levels were even lowered below the diagnostic threshold for CF. Across the board, about a 45\% decrease in sweat chloride levels were experienced due to the use of Ivacaftor versus little to no change in sweat chloride levels for patients given the placebo (see Figure 8).\textsuperscript{14}

Although the long term effects of Ivacaftor are still being studied, the obvious short term effects are hard to ignore. Ivacaftor could be a life saving treatment for CF patients with the G551D mutation. With so little research statistically proven, Ivacaftor could be a glimmering light not far from shore for CF patients. It has shown signs of improvement in the most fatal aspects of CF. It is now another possibility for patients with CF. Provided Ivacaftor’s ability to open up the chloride gate channels and allow ion movement around the body, fluid levels in CF patients can be relieved. With less fluid build-up in the lungs, infection rates will also decrease, lowering the mortality rate of CF. Ivacaftor could possibly be the greatest CF medical discovery to date. With continued research around Ivacaftor and its positive effects, soon it will help those who need it.
Conclusion

In the 1950s, few children with CF even lived to attend elementary school.\textsuperscript{1} With the advancement in healthcare, lifespan around the world has increased. The same goes for patients diagnosed with CF. Diagnostic imaging accounts for most of the diagnoses made today; for all illnesses. Since the 1950s there has been much information gained about the causes and effects of CF. CT scans have increased the quality of images providing greater detail into the body than ever before possible. The combination of X-rays and HRCT scans has revolutionized the scoring system for pulmonary degenerations. The Brody score is still the primary CF scoring system.

MRI has multiple advantages when used in diagnosing CF. MRI is best at visualizing soft tissue and the molecular difference between adjacent anatomy. This led to the realization that there could also be an abdominal connection between pancreatic abnormalities and CF. The use of MRI could see an increase in procedure diagnoses. Ultrasound is also starting to show its importance in diagnosis. The effects of CF manifest themselves in more places than just the lung tissue and abdominal regions. Dilation of the biliary tract is a common effect of CF and can be measured using ultrasound. Each modality plays its role in the diagnosis and treatment of CF.

Because early diagnosis is the best treatment for CF, children are being exposed to ionizing radiation at a very vulnerable age. Radiation is the most dangerous to cells that are rapidly dividing. For this reason, ionizing diagnostic exams need to be ordered only when the cost is outweighed by the benefit of the procedure. This is why ultrasound and MRI should be valued as the first choices, followed by X-rays and then CT scans. Unfortunately, CT scans usually provide the most detailed information.

Although there is no cure for CF, patients have a reason to hold onto hope for their future. With the discovery of the positive effects associated with Ivacaftor, relief is on the horizon. In the short term, pulmonary improvements as well as molecular equality in CF patients are allowing them to live normal lives. Long term studies are going to give researchers more information about how well Ivacaftor can reverse some of the side effects associated with CF, ultimately increasing life span. It will take more time, more money, and more research to get there. However, Ivacaftor leaves no doubt about its usefulness in taming CF symptoms. Regardless, medical advancements have allowed patients to live longer and healthier lives despite their disease.
References


Figures and Captions

**Figure 1.** A chest radiograph of a patient with cystic fibrosis. Tram-tracks can be seen radiating from the main bronchi throughout the bronchiole tree. The white striation throughout the lungs demonstrate thick mucus filling the bronchioles. Image courtesy of Cystic Fibrosis Imaging. Medscape Website. http://emedicine.medscape.com/article/354 931-overview. Accessed on October 20, 2013.
Figure 3. An abdominal MRI of an 18 year old girl with CF. The pancreas, indicated by the arrows, is greatly enlarged and shows signs of being completely replaced with fatty tissue. Researchers are still trying to find a possible connection between pancreatic atrophy and CF. Image courtesy of the American Journal of Roentgenology. Diagnostic imaging and related sciences. http://www.ajronline.org/doi/full/10.2214/AJR.05.0327. Accessed November 7, 2013.
Figure 4. An ultrasound of a 12 year old boy with CF. A dilated biliary duct is shown by the triangle arrowhead. A biliary artery indicated by the star captured. A portal vein indicated by the arrow can be studied. CF can cause biliary duct to dilation, possible strictures, and blockages. All can be seen using ultrasound imaging. Image courtesy of the American Journal of Roentgenology. Diagnostic imaging and related sciences. http://www.ajronline.org/doi/full/10.2214/AJR.06.1046. Accessed on November 7, 2013.
Figure 5. Shows the relativity of the most common imaging modalities and the relationship between their usage and their dosage. Radiographs are the most used modality but relative to its usage, has the lowest per procedure dosage to the patient. On the other side, CT has a low procedure rate but the highest amount of radiation dosage of any modality. Image courtesy of O’Connell OJ, McWilliams S, McGarrigle A, et al. Radiologic imaging in cystic fibrosis: cumulative effective dose and changing trends over 2 decades. Chest. 2012;141(6):1575-1583.
Figure 6. A graph of forced expiratory volume (FEV₁). Patients given Ivacaftor show +10.6% while the patients given the placebo show -0.2% change after 24 weeks. This is an animation of lung function. The greater the FEV₁, the more function is being recovered by the lungs. Image courtesy of Sermet-Gaudelus I. Ivacaftor treatment in patients with cystic fibrosis and the G551D-CFTR mutation. Eur Respir Rev. 2013;22(127):66-71.
Figure 7. The proportion of pulmonary event-free subjects are plotted against the amount of time that passed before their first pulmonary event. More patients using Ivacaftor were able to stay event-free for a longer period of time than patients on the placebo. This shows more effectiveness of Ivacaftor for CF patients with G551D mutations. Image courtesy of Sermet-Gaudelus I. Ivacaftor treatment in patients with cystic fibrosis and the G551D-CFTR mutation. Eur Respir Rev. 2013;22(127):66-71.
Figure 8. Sweat chloride concentration are measured over a 48 week period in CF patients. A base level of about 100mmol-L\(^{-1}\) for all patients. Patients given Ivacaftor show a fast and substantial decrease in sweat chloride levels after just 15 days. Patients given the placebo show no change in sweat chloride levels over the entire 48 week period. The dotted red line represents the diagnosable level of sweat chloride concentrations for CF patients. Image courtesy of Sermet-Gaudelus I. Ivacaftor treatment in patients with cystic fibrosis and the G551D-CFTR mutation. Eur Respir Rev. 2013;22(127):66-71.
### Tables and Captions

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