Symptoms and treatments in cystic fibrosis

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Abstract

Cystic fibrosis (CF) is one of the most common genetically inherited diseases which can cause premature death in western populations, with 1 in 2000-3000 new born babies being found to be affected by Cystic fibrosis in Europe [1]. The disease is caused by defective chloride ion channels along the epithelial membrane of the lungs, pancreas and other organs; although there are several hypotheses as to how this dysfunction specifically gives rise to the typical symptoms. The complications associated with the disease are varied, the most significant being the build up of abnormally thick excess mucus which can cause impaired function of the lungs and other major organs. Fortunately research into new treatments has significantly improved the life expectancy of people suffering from this disease.

This essay discusses the causes

Introduction

The name ‘ cystic fibrosis’ refers to the generation of cysts in the pancreas and the formation of excess fibrous connective tissue in the lungs.

The internal organs which suffer the most damage as a result of this disease are the lungs and the pancreas; although a variety of other organs are also affected.

The first clinical recognition of cystic fibrosis didn’t occur until the 1930’s when its symptoms were observed and characterised by Dr. Dorothy Anderson. The recessive nature of the disease was confirmed in the mid-forties after an investigation involving over one hundred families; although

the defective gene that causes the disease wasn’t isolated for another forty years when it was discovered in 1989 by reverse genetics. After the breakthrough in the forties general understanding of the disease increased steadily over the next couple of decades with a major clinical advancements in diagnostics occurring in the fifties with the development of the sweat test.

As cystic fibrosis is the result of an autosomal recessive disorder, the sufferer will have to of inherited two copies of the mutated gene (one from each parent) in order to be affected by the disease. The mutation takes place in a single gene on chromosome 7. This faulty gene leads to the development of a defective cystic fibrosis transmembrane conductance regulator (CFTR) protein. In healthy people the CFTR proteins form ion channels to transport chlorine ions across the epithelial membrane of the lungs, pancreas, sweat glands and other organs. It is also thought to regulate the activity of other chlorine-selective channels and some cation-selective (sodium ion) channels. Ions can then pass through these channels thereby maintaining the water potential of the cells. When the fine balance of ion concentration is affected less water is able to pass across the epithelial membrane by osmosis causing excess and highly viscous mucus to build up in the affected organs, resulting in severe long-term respiratory and digestive problems.

The human lungs are adapted for use in aerobic respiration by providing a thin, moist surface for gas exchange to take place between the pulmonary arteries and the external environment. For gas exchange to be effective the respiratory surface must comply with Fick’s law which requires that the surface area is large, moist and thin to enhance permeability. The resulting

fibrosis caused by the disease greatly affects the permeability of the lungs and hence reduces their capacity for gas exchange.

Molecular mechanisms

There are over 1500 types of mutation which can cause a defect in the CFTR protein, the most common of which is a deletion of phenylalanine at position 508 (âˆ†F508) which Is the cause of approximately two-thirds of CF cases. The mutations are categorised into six classes determined by their impact on the resulting functionality of the CFTR channels, ranging from reduced to complete non-function.

Class I, II and III mutations all result in the absence or substantial reduction of functional CFTR. Class I mutations cause a complete lack of protein production due to premature stop codons arising in the genetic code whereas class II mutations produce a protein that doesn’t fold properly and so is consequently degraded by the cell. In a class III mutation the lack of effective binding with ATP molecules leads to the defective regulation of CFTR and so again is classified as being non-functional. Classes IV and V still permit the development of functional CFTR albeit with reduced capacity for chloride ion transport or with reduced production of functional CFTR in general due to promoter mutations that decrease transcription [2]. Class VI mutations also produce functional CFTR although its degradation is greatly accelerated. The F508 deletion results in a class II mutation.

There are four main hypotheses as to how this defective gene causes disease although it is not known whether the disease is caused by one or a combination these hypotheses. Two of these, the low volume and high salt

hypotheses, provide a detailed description of the complications that arise as a result of faulty CFTR by taking into account the composition of airway surface liquid (ASL).

Low volume hypothesis

In the case of the low volume hypothesis it was postulated that there is little to no difference in the salt concentration of ASL between healthy people and those suffering from cystic fibrosis.

This hypothesis suggests that the symptoms of cystic fibrosis are caused by a dysfunction of the CFTR gene resulting in damaged or ineffective sodium ion channels. The damage caused is ergogenic and reduces the inhibition of the ion channels leading to the excessive movement of sodium ions from the ASL into the airways. The increased concentration of positively charged sodium ions in the airways then drives the absorption of chlorine ions and water, reducing the volume of ASL and dehydrating mucus. The dehydrated mucus becomes highly viscous and the cilia present on epithelial cells which are used to aid the clearance of mucus and to increase lung surface area become compressed by the mucosal build up. This compression of cilia inhibits the clearance of mucus which then continues to build up, further reducing the lung surface area. The excess mucus can also form hypoxic niches that can harbour colonies of pseudomonas aeruginosa.

Build up of mucus physically reduces the lung surface area affecting the efficiency of gas exchange. The mucus build up also increases the compression of cilia on epithelial cells which inhibits clearance by cilia and coughing.

High salt hypothesis

The high salt hypothesis assumes that the airway surface liquid of healthy individuals has a relatively low salt concentration when compared to the ASL of cystic fibrosis sufferers. It suggests that the symptoms of the disease are caused by the disruption or complete absence of CFTR function which causes excess sodium and chloride ions to be retained in the ASL. This increased retention of chloride ions leads to the ASL having an abnormally negatively charged composition. This abnormality impairs the activity of the body’s natural bactericidal enzymes such as lysozyme which rely on electrostatic interactions to attach to the bacterial cell walls; thus allowing bacterial infection to persist in the hypoxic niches formed within the lungs.

Abnormally high inflammation

It has been speculated that the defective CFTR itself may be the cause of excessive inflammation in the airways. However there is limited evidence to suggest that the defective CFTR is a cause of excessive inflammation in itself but rather that it interferes with the regulation of autophagy. Autophagy is the process by which defective proteins are degraded in order to maintain the balance between the recycling and synthesis of cellular products, for example the degradation of defective CFTR by the cells own lysosomes. Research indicates that large amounts of defective CFTR inhibits autophagy, leading to an accumulation of aggresomes which can cause inflammation in the lungs [3]. The resulting inflammation is what gives rise to the characteristic scarring of lung tissue.

CFTR bind with P. Aeruginosa

Chronic bacterial infection is common amongst all cystic fibrosis sufferers, specifically the bacterial species pseudomonas aeruginosa which binds readily to the CFTR protein. In healthy people the body initiates an immune response in order to fight off the infection. In cystic fibrosis suffers there is enhanced binding between p. Aeruginosa and the CFTR protein, the bacterium is also able to bind without initiating an immune response. The compromised immune response combined with reduced ability to clear mucus due to compressed cilia further increases the risk of severe infection.

Symptoms

Visible characteristics typical amongst suffers include a slightly meagre appearance due to inefficient absorption of nutrients and the famously salty sweat used to confirm CF diagnosis. Low levels of oxygen in the tissues due to impaired gas exchange between the lungs and the bloodstream can cause clubbing of the fingers and toes

Salty sweat

The salty sweat associated with the disease like so many of its symptoms is again caused by faulty CFTR present on the sweat ducts. As sodium ions leave the sweat ducts through ion channels chloride ions follow through them through the CFTR protein channels. However, in cystic fibrosis patients dysfunctional CFTR channels prevent the outward flow of chloride ions from the sweat ducts. The resulting high chloride ion concentration in sweat ducts creates an electrochemical gradient which “ pulls” more positively charged sodium ions into the ducts where the ions combine to form salt (NaCl). The salt is then secreted through pores in the skin resulting in very salty sweat

as very little NaCl is reabsorbed. Salt sweat concentration of greater than 60mEq/L is generally considered significant enough to make a diagnosis, although further test may be required.

Although poor growth can pose its own health risks the most severe symptoms are caused by the diseases capacity to cause damage to the internal organs.

Endocrine

CF is commonly referred to as an exocrine disorder meaning the resulting dysfunction affects glands which secrete their products through a duct to the surface of the body or of an organ, sweat glands and pancreatic ducts being an example of this. However some complications can arise in the body's endocrine glands, glands which secrete their product directly into the bloodstream. Disorders of the endocrine glands tend to affect the secretion of hormones. Damage to the islets of langerhans within the pancreas can impair the secretion of insulin which can eventually lead to CF related diabetes.

Pulmonary

Lungs are the predominant source of infection, vulnerable to different species of bacteria although P. Aeruginosa becomes predominant; eventually these bacterial colonies form a biofilm which is difficult to remove with antibiotic treatments. The thickening of mucus creates environmental niches suitable for harbouring bacteria. High levels of infection result in an inflammatory response which often leads to extensive tissue damage and scarring regarded as the characteristic fibrosis of the lungs. The resulting

fibrosis damages the epithelium of the lungs, making gas-exchange inefficient. Thick mucus also physically reduces the surface area

Implications for other organs

The lungs aren’t the only organs that suffer damage as a result of cystic fibrosis

Diverse range of other organs affected, majority of these form a part of the alimentary system

Lacking digestive enzymes in the intestines – Absence of these digestive enzymes impair patients’ ability to breakdown and therefore digest their food. This generally results in poor growth but in extreme cases can cause severe malnutrition.

Alimentary system – all digestive systems

The formation of cysts blocks ducts in the liver and pancreas preventing the secretion of essential digestive enzymes and hormones.

Blocked ducts prevent secretion of enzymes/hormones?

Mainly the pancreas which affects absorption of nutrients and can lead to poor growth in suffers

Blockage of ducts in the liver

New born babies can suffer from meconium ileus, an inability to pass their first faeces (meconium). The resulting ileus can cause blockages in the intestines that can cause rectal prolapse due to the strain involved in

producing a bowel movement. Common associations between cases of meconium ileus and CF led to it being used as a postnatal diagnostic technique.

Excess viscous mucus isn’t only a problem in the lungs. Organs of the alimentary system can also be affected. Thick mucus can block pancreatic ducts preventing the secretion of vital digestive enzymes into the duodenum. The body is then unable to effectively extract nutrients from the ingested foods. Malabsorption is a common symptom of CF generally resulting in poor growth but in extreme cases can cause severe malnutrition.

Fertility problems

Fertility problems related to CF usually occur before birth whilst the foetus is still developing.

Blocking of or complete absence of the connective tube (vas deferens) between the testes and ejaculatory ducts in males means that although they are not sterile they are unable to conceive children by traditional intercourse. In women thick mucus can cause blockages in the cervix or their ovulation cycle may be disrupted malnutrition as a result of CF related enzyme deficiencies. More than 95% of males with CF are infertile.

Percentage of CF infertile – source world health organisation

Treatments

Unfortunately there is currently no cure for CF however there are several treatments that can alleviate some of the symptoms associated with the disease, such as the use of hypertonic saline and enzyme replacement.

Treatments such as gene therapy are more geared towards creating a permanent cure for CF, although at this moment in time the technology has not been perfected.

Pharmacological treatments

Fortunately the CFTR's are not the only chloride ion channels available on lung surface epithelium. Certain drugs can stimulate these other channels. Rcjournal.

Stimulate the release of calcium or inhibit sodium channels to offset negative effects of whatever hypothesis.

Hypertonic saline

Major complications of CF stem from the imbalance in ion concentrations caused by the faulty CFTR gene. From this knowledge a line of treatments were developed in order to restore the ionic imbalance and hence improve the body's ability to clear thick mucus from the lungs. The answer would need to be a sterile solution; high in salts that could be inhaled to replace the ions which weren't being transported across the CFTR channels. The solution, hyper tonic saline, is a cheap and effective treatment for reducing the viscosity of mucus in the lungs. After it is inhaled the solution works by creating an osmotic gradient, drawing water into the airways, rehydrating the mucus causing blockages and reducing its viscosity hence making it easier to cleared and coughed up.

Enzyme replacement

Enzymes can be *injected* to restore the deficiency created by blockages of pancreatic ducts. Patients undergoing enzyme replacement therapy can

expect to see improvements in growth, weight gain and general health as many illnesses arise from poor absorption of nutrients. Nutritional supplements can also be taken to replace those not being absorbed normally.

Important short term treatments are giving nutritional supplements to sufferers to relieve malnourishment and promote healthy growth

Nutritional plans generally involve high calorie diets rich in vitamins such as vitamin D to develop strong bones and prevent osteoporosis.

Gene therapy

Soon after the discovery of the defective gene in 1989 efforts were invested in finding a therapy that could target the disease at its genetic roots. Discovery of an effective method of gene therapy would open a virtual goldmine in treating not only cystic fibrosis but also other genetic diseases.

One of the current gene therapy techniques for the treatment of CF involves the use of adenoviruses carrying vectors containing corrected copies of the CFTR gene.

The adenoviruses carry double stranded DNA which is deposited in the nucleus of the host cell and then transcribed in the same way as the host cells own DNA. However, as this is an example of somatic gene therapy, the DNA of the adenovirus won’t integrate with the host genome and the gene will not continue to be expressed after cellular division. This means the effects are not permanent and patients will require subsequent treatments to maintain the effect. There are of course risks associated with the use of

viruses to incorporate functional DNA. Even though the viruses being used are non-pathogenic the presence of a foreign body can still initiate an immune response; the resulting inflammation can be dangerous for patients who are already at high risk of excessive inflammation due to immunocomprimisation. An alternative to adenoviruses are adeno-associated viruses (AAV). AAV vectors are non-pathogenic and have been shown to have a lower prevalence to neutralising antibodies when compared to adenoviruses in vitro [4]. However they do have a relatively small genome of ~4. 8 kilobases, with most gene treatments requiring the complete replacement of the viral genome.

As a result of this, research is being targeted towards more effective means of gene therapy with tests being carried out with AAV and lipid-vectors. There is a trade off between the effectiveness of the method used to induce the vector. Viral vectors are more effective at integrating the vector into the host DNA compared to lipid vectors, but there is the increased risk of an immune response.

Lung transplant

In the most severe cases where patients are suffering from chronic infection lung transplants can be carried out where appropriate. In these cases both lungs need to be transplanted in order to prevent the new lung from being contaminated by existing bacterial populations currently present in the patient.

Antibiotics

Antibiotics tend to be used prophylacticaly as a pre-emptive measure for preventing infection.

One common type of drugs used in treatments are macrolide antibiotics – can suppress obstructive secretions in airways

The macrolide antibiotics work by binding to the 50s subunit of the bacterial ribosome, thereby inhibiting protein synthesis.

Conclusion

The overall outlook for patients with CF has improved dramatically over the past eighty years since the first clinical recognition in the 1930’s. A greater understanding of genetics has enhanced both the fields of clinical diagnostics and treatments. The future of treatments points towards gene therapy, we currently have the technology to do this but further research is needed to overcome the major obstacles such as more efficient transfer and getting the gene expression to last longer.

[*http://www. who. int/genomics/public/geneticdiseases/en/index2. html#CF]

http://www. medscape. com/viewarticle/576200_2

http://www. nature. com/ncb/journal/v12/n9/full/ncb2090. html

http://www. nature. com/gt/journal/v6/n9/full/3300994a. html

Figure 1. Sweat chloride concentrations related to cystic fibrosis (CF) diagnosis. Revised and reprinted by permission from Davis PB. Cystic fibrosis. Pediatr Rev 2001; 22: 257-264. Figure 1