Research Article

Management of Cystic Fibrosis – Challenges in Pakistan

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Abstract:

Background: The objectives of this study were to find out frequency of Cystic Fibrosis among children who presented in our tertiary care hospital with triad of diarrhea, pneumonia and failure to thrive, to find out appropriate investigations and availability of medicines and tools for physiotherapy. This will help to understand the burden the of disease in Pakistan. Method: This was a cross sectional study conducted over a period of one year from October 2016 to September 2017 at Liaquat National Hospital Karachi. The inclusion criteria was children with repeated chest infections, diarrhea and Failure To Thrive (FTT); criteria for FTT was anthropometric measurements below third centile. Children with any other known or diagnosed pathology e.g. TB or immunodeficiency were excluded. Diarrhea was considered as per WHO definition: The passage of 3 or more loose or liquid stools per day, or more frequent than is normal for the individual.Criteria of diarrhea was based on relevant history from mother. Pneumonia is defined as: Acute infection of lung parenchyma by one or co-infecting pathogens. As cough and fever are the most common presentations, so relevant history in the past were used for possible pneumonia. However chest x-ray was done for similar presenting complaints.

Results: Sweat for the estimation of chloride was possible to collect in 89 out of 105 (84.76%) children. Sweat chloride was significantly high i.e. $\geq$ 60 mmol/L in 20 (22.47%) while normal in rest 69 (77.53%) children. $\triangle$ 508 was sent in 34 out of 105 (32.38%) children. It was detected in one patient (2.9%) and negative in rest of 33 (97.1%). Stool elastase was done in 49 out of total 105 patients (26.66%). It was significantly low i.e. <200 mcg/Gm in stool, in 10 (20.4%) while normal in 39 (79.6%) children. Immuno Reactive Trypsin or IRT, is not available throughout the country Basic drugs needed to cover ongoing infections were available in oral, parenteral and inhalation formulation but advance modalities were not found. Conclusion: Cystic Fibrosis is an under diagnosed disease in Pakistan as many cases were being treated symptomatically only. Improving sensitization among doctors, diagnostic facilities and treatment options can offer our patients a better survival and quality of life.

Key words: cystic fibrosis, diagnosis and management, data from Pakistan and world.

Introduction

Cystic fibrosis (CF) is known since long but recognized as a disease after 1930 only[(1)]. It was well recognised that if a child is 'salty' on kissing, will not survive long. In 1936, G Fanconi described connection between pancreatic malfunction and bronchiectasis[(2)] Dr Dorothy in 1938 mentioned characteristic findings of cystic fibrosis of pancreas and its correlation with intestinal and lung disease. She also hypothesized the autosomal recessive nature of the disease and described need for pancreatic enzyme replacement for the treatment[(3)].Sweat chloride

abnormalities were discovered in 1953[4] and diagnostic technology was greatly improved over next decade. In 1989, abnormal gene was localized at chromosome number seven[5]; till now more than fifteen hundred genetic abnormalities have been identified which may be responsible for the range of signs and symptoms with which a patient can present.

Cystic Fibrosis is a genetically transmitted life limiting disease. The inheritance is autosomal recessive, so is transmitted by and presents both in males and females. It is caused by a mutation in Cystic Fibrosis Trans-membrane Conductance Regulator (CFTR) gene located on chromosome number seven. This CFTR gene produces chloride ion channel which controls chloride and water contents of sweat, pancreatic enzymes and mucus production especially in intestine and lungs. Malfunction of the gene may result in chloride lost in sweat and thick mucoid secretion mostly effecting lungs and intestine. Thick secretions in the lungs block the airways leading to infection starting from early life. Similarly thick pancreatic and liver secretions block the ductal system of these organs resulting in malabsorption. Later on there may be infertility or reduced fertility due to blocked vas deferens ducts in males and thick vaginal secretions in females[6-8].

CF may present from the newborn period. Delayed passage of meconium or meconium ileus should raise the suspicion. Any child with repeated chest infections, chronic diarrhea with oily stools and failure to thrive deserves investigations for Cystic Fibrosis.

The disease is common in western hemisphere of globe but not uncommon in other parts of the world as well. Western data shows carrier frequency of 1:25 and disease incidence of 1:2500[8]. Large population size and preferred trend for interfamily marriage may account for high incidence and prevalence of this disease in Pakistan[9-11]. However no local data is available regarding disease burden. There are limited diagnostic and treatment facilities which are available in only larger cities of the country.This may be adding to unrecognized morbidity and mortality in children possibly suffering from this condition.

Patients and Method

This was a cross sectional study conducted in the Pediatric ward and Out Patient Department of Liaquat National Hospital, Karachi, a tertiary care hospital and teaching institute, over a period of one year from October 2016 till September 2017. The inclusion criteria was children admitted in ward or presented in outpatient department with history of repeated episodes of diarrhea and pneumonia along with failure to thrive (FTT). Criteria for FTT was height and weight below third centile on growth chart. Patients fulfilling the criteria were worked out for common causes like Cystic Fibrosis, TB and immunodeficiency. Children diagnosed with tuberculosis, dietary mismanagement or immunodeficiency were excluded from the study.

A total of 105 children fulfilled triad of eligibility criteria. A tabulated performa was filled by residents, with patient's name, medical record number, age, sex, presentation and tests done. Tests included were sweat chloride, △ 508 and stool for elastase along with base line investigations. Immuno Reactive Trypsin (IRT) was not found being done anywhere in the country. Sweat chloride remains the gold standard for the diagnosis of CF. This test measures the amount of chloride in sweat. Sweat production is stimulated by iontophoresis and sweat is collected on a specialised filter paper. When required amount of sweat is collected usually in 30 minutes time then amount of chloride is estimated in sweat. In some patients, 16 out of 105 (15.24%) for technical reasons, mostly small size of the child, it was not possible to collect required amount of sweat for estimation of chloride.

Similarly, in many cases for reasons, mostly financial, it was not possible to send △ 508 gene mutation and stool for the measurement of elastase in laboratories outside the hospital, which were doing these tests.

Results of available investigations were analysed to find out optimum tests needed for the confirmation of diagnosis.

A list of necessary therapeutic items was generated and market was surveyed by residents for their availability and price. Items included were medicines, inhalers, nebulizers and instruments for chest physiotherapy. This helped us to formulate recommendations for the optimistic and optimum management of a chronic disease like cystic fibrosis.

We also searched for affordable alternatives food items on which pancreatic enzyme supplements (Creon) can be sprinkled, that an average family with a chronically sick child can afford every day, five times daily[20].

Results

Children who presented with repeated chest infections, diarrhea and failure to thrive, their bio-data was analysed. (Table 1). Results of tests performed to confirm the diagnosis of cystic fibrosis were compiled and analysed (Table 2). Sweat chloride remained gold standard for the diagnosis of Cystic Fibrosis. However in many children, especially if they presented early in life, it was not possible for reference laboratory to collect enough sweat for the estimation of chloride level. Sweat chloride was significantly high, i.e. $\geq$ 60 mmol/L, in 20 out of 89 children (22.47%). Main limitation was collection of optimum amount of sweat from a small baby i.e. 75 mg or 15 µL of sweat.$\triangle$ 508 was detected in 1 out of 34 patients tested for this mutation (2.9%), so it can only be a supplementary test. Test negative for this mutation cannot rule out Cystic Fibrosis in Pakistani population, which may have other mutations, reason for negative classical $\triangle$ 508 and variability of symptomatology. Results of stool elastase, a non-invasive test, were encouraging. It was positive in 10 out of 49 samples (20.4%). So far this test is being done by one laboratory only. Immuno Reactive Trypsin (IRT), a valuable test for neonatal screening with dried blood spot on Guthrie cardis not available in Pakistan. Similarly availability of drugs and accessories were searched; basic drugs like antibiotics, respiratory solutions and inhalers were freely available. But advance modalities like instruments for home chest physiotherapy, which can improve the survival and quality of life, were not found in local market.

Discussion

Cystic Fibrosis is genetically transmitted on Autosomal Recessive base[8]. Pakistan ranks number six in the list of countries by population[11]. Interfamily marriages are preferred especially in rural areas among less resourced and less educated families. Incidence is about 63% on an average while it was found 83.3% in parents having children with Cystic Fibrosis[9,10]. Keeping in view these demographic facts, burden of the disease may be immense. Due to logistic reasons like any resource poor or mal-distributed country, there are no authenticated facts and figures regarding incidence or prevalence of Cystic Fibrosis[12-16].But malnourish children with repeated episodes of diarrhea and pneumonia are not uncommon in clinical practice. Due to lack of facilities and orientation for diagnosis, such children are usually treated symptomatically. This leads to high morbidity and mortality on one hand and frustration in parents and physicians on the other hand. Diagnostic facilities like Immuno Reactive Trypsin (IRT) for new born screening are not available which can help in the screening of a neonate born in a family with a child already diagnosed with cystic fibrosis[17]. It helps to confirm the diagnosis at the earliest and avoid unnecessary investigations. IRT test is easy to establish as sample is collected from neonatal heal prick on Guthrie card as dried blood spot. This card with patient's details can be sent to a central reference laboratory by ordinary mail. Similarly result can be sent back to referring hospital by mail to referring hospital. This is the responsibility of concerned hospital to immediately contact family and arrange consultation with Pediatrician for management and family counseling. Sweat chloride testing is the gold standard test for the diagnosis of Cystic Fibrosis so for[18]. It is available at larger tertiary hospitals in big cities like Karachi, Lahore and Rawalpindi only. Collection of required amount of sweat for chloride estimation is a practical problem especially in small children.

There are more than fifteen hundred genetic mutations described leading to Cystic Fibrosis. This may be responsible for variable presentation of disease in different patients. Some studies have shown only 17% incidence of △508 in Pakistani population[12], most common mutation in northern Europe and America. This means majority of Pakistani patients have other mutations of CFTR gene. There is work in progress at National Institute of Blood Diseases (NIBD) Karachi on finding out common gene mutations in patients with Cystic Fibrosis; we are looking forward for the results which will help to construct a panel of local gene mutations[19]. Treatment facilities are available in tertiary care hospitals of large cities. As shown in table 3, most of the basic drugs like antibiotics, multivitamins and bronchodilators are available. However some therapeutically important drugs and tools needed for state of art management are not available. This can negatively affect the prognosis of the disease. Orientation among health care provider is an important factor in the management of Cystic Fibrosis. When a pediatrician or general practitioner suspects or keeps Cystic Fibrosis in differential diagnosis, only then investigations are asked to confirm or rule out this condition. Once diagnosis is confirmed, multidisciplinary management approach is started which needs facilities available preferably under one roof and good coordination among different disciplines like pharmacy, nutrition and physiotherapy etc. A pediatrician with special interest in Cystic Fibrosis is the team leader and a dedicated nurse helps to coordinate different services and guide the patient and family.

Cystic Fibrosis is a disease which involves multiple organs notably liver, pancreas, intestine, lungs and skin, leading to high morbidity and mortality. Management needs multidisciplinary approach where Pediatrician is the team leader assisted by pulmonologist, gastroenterologist, pharmacist, nutritionist, physiotherapist, respiratory nurse, psychiatrist, social worker and pediatric surgeon on board. Pakistan is a resource mal-distributed country where most of the patients themselves are responsible for their treatment. At times it becomes difficult, if not impossible for a low to middle class family to treat a financially and logistically demanding chronic disease like Cystic Fibrosis for which so far no curative treatment is available. Social services are of great help during socially and financially difficult times which affected families face not infrequently.
As mentioned in table 3, although basic drugs are available, many crucial items are not available in Pakistan, e.g. Capsule Creon is available but Creon granules with measuring spoon are not available. This spoon gives accurate measurement of drug in case of small children; spillage and wastage could also be avoided. Proper combination of multivitamins is important as it is convenient for both parents to administer and patients to swallow. Real challenge faced by Pediatrician is how to properly administer Creon. Creon is the proto brand of pancreatic enzymes, which needs to be active in intestine only [8]. This should be administer before feeds; full dose with 3 main meals and half dose with two snacks in between major meals; so frequency of administration is five times a day. In pre-weaned children measured dose can be sprinkled over a small spoon of milk, followed by water intake to wash the oral cavity of any granule sticking there which can cause oral ulceration. Full feed should be given after drug administration. If child is weaned, then required amount of granules can be sprinkled over a soft mildly acidic food taken in a spoon. Child should swallow sprinkled granules without chewing, followed by water drinking to clean the oral cavity and then having meal. Older children can swallow capsule before meals. Recommended food for granule sprinkling is apple sauce[8], which is difficult for an average Pakistani family to offer their child five times a day, till child can swallow a capsule. Research showed many easily available local foods with similar consistency and PH[20] e.g. yogurt.

Energy dense homemade tasty food should not be a problem but mothers need orientation. Kitchri, daleem, harees and pakora etc are good example of multi-mix energy rich foods. Children should be encouraged to take a small bowl of simple mixed salad to fulfill their daily requirement of vitamins, mineral and fibers.

Children with Cystic Fibrosis need frequent administration of antibiotics. Choice of antibiotic depends upon the age and condition of children. At an early age they are more prone to gram positive staphylococcal sino-pulmonary infections. Grown up children show respiratory tract infection with pseudomonas leading to irreversible bronchiectasis. Burkholderia Cepacia is the organism which rapidly declines lung functions[7,8]. Rout of antibiotics depends upon severity of involvement of body systems. For example milder throat infection

can be controlled with oral antibiotics while severe lung infections need intravenous rout for longer duration. Infections localized to lung scan be eradicated with suitable inhaled antibiotics, avoiding systemic side effects. Most of the recommended antibiotics for Staphylococci, Pseudomona and Burkholderia were found easily available both in oral and parenteral formulation. Useful drugs for suspected Staphylococcal infection are Linezolid, Clindamycin, Amoxicillin-clavulanate and Vancomycin. Infections with Pseudomonas can be sensitive to Imipenem, Meropenem, Ceftazidime, Piperacillin-tazobactam, Amikacin and Tobramycin; Meropenem is also effective against Burkholderia. Tobramycin is the only available inhaled antibiotic[8] in Pakistan,however goodor equivocal results are seen with regular intravenous preparation of Amikacin andColistimethate / Colomycin used for inhalation in parenteral doses.

Ivacaftor[25,26] is an orally administered drug which potentiates function of mutatedCystic Fibrosis Trans-membrane Conductance Regulator (CFTR) gene. This improves the lung and gut functions and helps in weight gain. This is recommended after six year of age. However this is not available in Pakistan.

Other practical issue is the availability of age appropriate instruments of physiotherapy. Lung pathology is the main reason behind morbidity and mortality. Bronchodilators open up the lung passages while inhaled antibiotics act locally on the non-invasive lung pathogens. Drainage of secretions and pathogens is probably as important which depends upon lung physiotherapy[21]. Chest physiotherapy (CPT) cups are effective and easy to use if parents are properly trained. After bronchodilator inhalation, either with Meter Dose Inhaler (MDI)or nebuliser, physiotherapy is done to dislodge and expectorate infected lung secretions of bronchiectasis. This is best done in head down position with chest at a higher level. This may be done with the help of a pillow under child's chest. Child is either in lateral or prone position to facilitate expectoration of infected bronchial secretions. Antibiotic is nebulized after physiotherapy for best results. Similarly bubble blowing rings can be made available, an exercise children enjoy as a game. This opens up collapsed lung alveoli and bronchioles and helps in slowing down of process of bronchiectasis.

For the care of patients with Cystic Fibrosis in Pakistan a lot of work is needed from the grass root till highest level. First and most important is sensitisation and orientation among the doctors. This can be done through teaching at under and post graduate levels, sharing local experience (like this article) and emphasis on keeping Cystic Fibrosis in differential diagnosis of patient presenting with repeated episodes of diarrhea, pneumonia and failure to thrive. Diagnostic facilities should be available widely. Cystic Fibrosis Trans-membrane Conductance Regulator (IRT) screening[17] is done through heel pricked Guthrie card which can be transported through mail at designated center. To start with such a center may be established at Islamabad. A baby born to index patient's family or in a family with infantile death where history is suggestive of Cystic Fibrosis should be screened in the first week of life.

Sweat chloride test is easy to establish if technicians are properly trained. This test should be available in tertiary care hospitals, teaching institutes and reliable regional laboratories. It is sometimes difficult to collect required amount of sweat especially in a small child. May be we have to address this issue in a different way. Pakistan is a sunny country. After good hydration, children can be exposed to hot environment, while under observation, like in a shade outside the ward, to collect sweat in a plain tube. Chloride can be estimated from this sweat like serum chloride level. This is easy, practical and economical method with immediately available results. Finding out common local mutation is very important both for diagnostic and therapeutic point of view. It is hoped that work on genetic mutations will soon start in Karachi[19]. Sometimes different mutations have different clinical presentation and response to treatment. For example, a child mainly presenting with respiratory signs and symptoms but minimal gastroenterological manifestations can be a variety of Cystic Fibrosis due to different gene mutations. Orientation of local patterns helps to clinch the diagnosis with some different presentation. Treatment options may also need to modify according to predominant organ involvement, lung, liver or gut. Regarding treatment, Creon the pancreatic enzymes are available in Pakistan. Creon is available in Capsular form

only but for young children granules with spoon are preferable for accurate measurements. Creon granules with accompanying measuring spoon are not available but needed for precise dose in infants. Instrument for physiotherapy are as important as drugs; they should be available in tertiary care centers. Much needed instruments are bubble blower and Chest Physio Therapy (CPT) cup. They help in opening up lung alveoli and bronchioles and drainage of infected secretions. Physiotherapy is partner in the management of bronchiectasis with antibiotics. Dedicated physiotherapists can train parents and grown up patients for home management. This is convenient for families and gives good results due to compliance. Literature and leaflets for parents describing the disease and its management in simple Urdu should be easily available both in wards for admitted patients and in Out Patient Department for short visiting patients. These publications should have colored pictures. Colored photographs help parents and physicians to recognise inhalers which have universal color codes e.g. salbutamol / ventolin is always bluish gray in color or Fluticasone / Flixotide is orange colored. Leaflet also highlights maintenance of instruments like how to clean aero chamber. Sick day rules are also written on this paper and are explained to parents. Such a leaflet has been developed by our team and can be provided on e-mail request sent to author.
Last but not least, there should be a social welfare department to help the families if there are socio-economic hardships; counselors help them to stick with regime.

Table 1: Bio-data of patients with Cystic Fibrosis

S N	Character	Value
1	Total number of patients	105
2	Male	65 (62%)
3	Female	40 (38%)
4	Age on admission:	
	Range	4 month – 5 year
	Average	20 month
	Median	18 month

Table 2: Analysis of diagnostic tests done for the diagnosis of Cystic Fibrosis (n = 105)

S N	Investigation	Total	Positive	Negative
1	Sweat chloride	89 (84.76%)	20 (22.47%)	69 (77.53%)
2	Delta 508	34 (32.38%)	1 (2.9%)	33 (97.1%)
3	Stool elastase	49 (46.66%)	10 (20.4%)	39 (79.6%)

Table 3: Availability of items needed for the management of Cystic Fibrosis

No	Name of drug/item	Strength	Availability	Remarks
1	Capsule Creon[8] *	2500, 3000, 5000, 10000 IU	Yes	
2	Creon – micro granules		***No***	For infants
3	Apple sauce ** Yogurt – alternative	Spoonful for each dose	Yes Yes	Expensive Economical
4	Multivitamin – Syrup Abdeks/ ml –Drops Abidec / 0.6 ml	 A-5751, D-600, K-400, E-50 A-1333, D-400, B-10, C-40	Yes	
5	Vitamin A	2666 iu/drop	Yes	
6	Vitamin D	400 iu /drop	Yes	
7	Vitamin E	Syrup – NA ***	Yes	On request
8	Vitamin K	Syrup – NA ***	Yes	On request
9	Inhalers: - Salbutamol - Beclomethasone - Fluticasone -Salmeterol+ Fluticasone -Salbutamol+ Beclomethasone	Mcg / puff Ventolin (100) Beckson (50) Flixotide (50, 125, 250, 500) Seretide (25+50,125,250) Xaltide (100+50)	Yes	
10	Nebuliser machine Respiratory solutions: -Salbutamol -Beclomethasone -Ipratropium	 Ventolin (5 mg/ml) Clenil aerosol (400 mcg/ml) Atem, Ipratec (250 mcg/ml)	Yes	
11	Hypertonic saline[22]	3%, 5%, 7%	Yes	
12	N-Acetyl Cysteine[23]	10%	Yes	
13	Dornase alpha[24]		***No***	Adjuvant
14	Antibiotics[8]	Oral, IV, respiratory solution	Yes	
15	Ivacaftor[25]	Oral	***No***	New ****
16	CPT cup	For chest physiotherapy[21]	***No***	For infants^
17	Bubble blower	For chest physiotherapy	***No***	Economical^
18	Chest vibrator		***No***	Effective
19	Chest wall Oscillator		***No***	Effective
20	IRT[17]^^		***No***	For infants

* Creon – pancreatic enzymes: lipase, protease, amylase; strength mentioned is for lipase
** Apple sauce is soft mildly acidic food over which Creon granules are sprinkled;
*** NA – Not available. **** CFTR potentiator, given PO
^Can be produced locally. ^^ Immuno Reactive Trypsin

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