INTRODUCTION

Cystic fibrosis (CF) is life limiting genetic disorder common in Caucasians of North America, Australia and Europe.\(^1,2\) Mutated CF transmembrane conductance regulator (CFTR) epithelial chloride channel desiccates secretions in respiratory airways, hepatobiliary-pancreatic ducts and in other tissue linings, resulting in gradual and persistent organ damage.\(^3\) Estimated gene frequency of cystic fibrosis...
Profile of Cystic Fibrosis children varies in different ethnic groups with highest incidence in Caucasians (1 in 2,500). Approximate incidence of CF in South Asians immigrants settled in UK is about 1:10,000 to 1:12,000. CF is one of the under diagnosed disease in Pakistan. Case identification on basis of history, examination and relevant laboratory investigations are fundamental for successful diagnosis.

Patients with CF usually present in the first two years of life with chronic productive cough, recurrent pneumonia, resistant asthma, failure to thrive, chronic diarrhea (steatorrhea) and dehydration. Neonatal Screening program measuring activated serum trypsinogen level has been conducted in developed countries to pick the potential cases early in life. In underdeveloped countries, screening programs are not available and most of the cases are diagnosed on the basis of clinical presentation and supported by sweat chloride test and genetic analysis. Genetic diagnosis in CF is crucial in defining the disease behavior and prognosis. Most commonly reported CF related genetic mutation among Caucasians is Delta F-508. Limited range of genetic mutation analysis is available in our part of world. Mutations data reported in few studies in Pakistani CF suggested that D-F508 mutation is rare in this population. This is in contrast to some studies which showed predominance of this mutation in Pakistani community with CF.

Aim of this study was to highlight the main clinical features seen in CF children in our population and pertinent laboratory workup done to diagnose and manage these patients.

METHODS

A three years retrospective study conducted at Aga Khan University Hospital from January 2013 to December 2015 after approval of Ethical review committee of the university. Admitted patients diagnosed with Cystic fibrosis on the basis of their clinical features and positive sweat chloride test from birth to 15 years of either gender were enrolled in this study. Patients were categorized in five groups for the age at the onset of symptoms and age at diagnosis. These CF patients were studied further for their initial clinical signs or symptoms. Sweat chloride values were noted for their mean value and standard deviation. Sweat was stimulated by means of pilocarpine iontophoresis and sweat collection done by Wescor macroduct sweat collection system as adopted by chemical pathology laboratory of the hospital. Patients with sweat chloride values more than 60mmol/L were labeled as positive and consistent with diagnosis of CF. Around a decade ago, Delta F-508 mutation analysis was started at Aga Khan University Hospital molecular laboratory on the basis of reported genetic mutations in CF Children from our adjoining region. All patients with positive sweat chloride were analyzed for Delta F-508 genetic mutation. Patients with positive Delta F-508 gene mutation status were further categorized in homozygous and heterozygous. Family history or history of siblings with CF was noted along with parents who have consanguineous relations. General body parameters were noted along with common physical examination findings. Neonatal, respiratory, gastrointestinal, cardiovascular and other presentations were documented for these children.

Complete blood count, Electrolytes, stool for fat globules, Blood culture, and X rays findings were noted. High resolution Computed Tomography scan (HRCT) of chest done at the time of diagnosis were studied and categorized into six different categories according to radiological findings. Sputum for organism growth was studied further to find out first organism to colonize the airway at the time of diagnosis.

Results were analyzed using SPSS version 20. Data was summarized using mean, standard deviation, numbers and percentages for different variables.

RESULTS

This study enrolled 43 children with clinical features suggestive of Cystic fibrosis and with positive sweat chloride test. Mean age in our population was 56.00±33.71 months (4.6 years). Male to female ratio was 1.3:1. Different demographic feature of our population are shown in Table-I. Family history was positive in four patients (9.30%) and 24 (55.81%) children have parents with

| Table-I: Demographic Features and General Parameters of CF Children (N=43). |
|---------------------------------|-------------------------------|
| Age in months                  | Mean: 56.00 months, Std. Deviation: ± 33.71, Range 1 month -178 months |
| Male                           | 25 (58.13%)                   |
| Female                        | 18 (41.86%)                   |
| Male to female Ratio          | 1.3 : 1                       |
| Mean age at onset of symptoms | 14.41± 26.18 months           |
| Mean age at diagnosis         | 47.20 ± 45.80 months          |
| Height below 3rd centile      | 24 (55.81%)                   |
| (short stature)               |                               |
| Weight below 3rd centile      | 34 (79.06%)                   |

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consanguinity. Comparison of different age groups for onset of symptoms and diagnosis is shown in Fig-1. Different diagnostic test done in our patients are presented in Table-II. Chronic cough was the most common initial clinical presentation in our experience. (Table-III), Clinical presentations noted in our cohort including neonatal, respiratory gastrointestinal and hepatobiliary systems are presented in Fig-2. Results of different investigations done on CF patients are shown in Table-IV.

DISCUSSION

Cystic fibrosis (CF) is one of the underdiagnosed inherited diseases in developing countries. Clinical features in CF are similar to common respiratory and gastrointestinal diseases and may mimic with asthma, pneumonia and malabsorption syndromes. At the same time, high under five mortality rates in our region has overlooked CF being one of the potential differential diagnoses in such children presenting with respiratory infections and diarrhea. This delay is partly due to lack of rationalizing CF by health care provider as an important differential diagnosis and partly by non-availability of facilities assisting early diagnosis. More than half of our cohort had parents with consanguineous marriages which is similar to Desgeorges M et al. from Lebanon who found 50% rate of consanguineous marriage in their CF population.

More than 1800 mutations have been reported for CFTR gene. In our study, (27.90%) patients have shown positive results for Delta F-508 genetic mutation with 5 (11.62%) were heterozygous and 7 (16.27%) were homozygous. This is consistent with Kabra et al. and Naguib et al. which shows similar results with positive delta F508 mutation seen in 19% and 25% patients respectively. Similarly, the previous data from Pakistan showed that the frequency of delta F508 mutation in Pakistani CF children is lower than reported frequency in the Caucasian population.

The most common first ever clinical presentation in CF children in our population was chronic cough that was noted in 30 (69.76%) patients followed by chronic diarrhea. One patient presented only with failure to thrive in absence of associated respiratory or gastrointestinal features. Four (9.30%) patients had meconium related presentation at early neonatal

### Table-II: Diagnostic Tests in CF children.

| Test                        | Mean Value | Std. Deviation |
|-----------------------------|------------|----------------|
| Sweat chloride test results| 82.70      | ± 22.74        |
| Gene analyses for Delta F-508 | 12 (27.90%) |                |
| Negative for Delta F-508    | 31 (72.09%) |                |
| Heterozygous                | 5 (11.62%)  |                |
| Homozygous                  | 7 (16.27%)  |                |

had symptoms in first year of life and diagnosis was made after second year of life. This delay is partly due to lack of rationalizing CF by health care provider as an important differential diagnosis and partly by non-availability of facilities assisting early diagnosis. More than half of our cohort had parents with consanguineous marriages which is similar to Desgeorges M et al. from Lebanon who found 50% rate of consanguineous marriage in their CF population. More than 1800 mutations have been reported for CFTR gene. In our study, 12 (27.90%) patients have shown positive results for Delta F-508 genetic mutation with 5 (11.62%) were heterozygous and 7 (16.27%) were homozygous. This is consistent with Kabra et al. and Naguib et al. which shows similar results with positive delta F508 mutation seen in 19% and 25% patients respectively. Similarly, the previous data from Pakistan showed that the frequency of delta F508 mutation in Pakistani CF children is lower than reported frequency in the Caucasian population.

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age. Meconium Ileus is frequently described as a significant clinical evidence for CF and these infants should be screen promptly as advocated by Sawicka et al. from Poland and Mushtaq et al. with East London experience. Two (4.65%) patients presented with electrolyte imbalance with pseudo barter syndrome as their first CF defining feature. Metabolic alkalosis with electrolyte imbalance is one of the noteworthy clinical presentations in children with CF, especially in humid areas and timely investigations can help to establish appropriate diagnosis.

Chronic productive cough was present in 39 (90.6%) patients being the most common clinical presentation in our population. About 31 (72%) patients had recurrent bronchopneumonia and 19 (44.18%) patients had chronic cough with wheezing requiring bronchodilators and inhaled steroids. Childhood wheezing in CF is frequently reported and is associated with poorer lung function at later age. Patients with CF are at augmented possibility of having nasal polyps and rhinosinusitis. In our experience, 6 (13.95%) children with CF had nasal polyp and 5 (11.62%) had chronic rhinosinusitis. Pulmonary hypertension is associated with considerably high risk of mortality in CF patients especially with progressive pulmonary disease. Thirteen (30.23%) patients in our cohort had moderate to severe degree of pulmonary hypertension documented on two dimensional Doppler echocardiography.

Gastrointestinal manifestation in CF is related to some important mutations and its presence or absence along with its onset has been demarcated by different genetic mutations. Our study has documented 5 (11.62%) patients who had presented only with steatorrhea as the onset of CF defining symptom and around 24 (56%) patients had this presentation in the course of of their illness. These findings are similar to Kawoosa et al. who found

### Table-IV: Laboratory and Radiological Investigations (N=43) in CF patients.

| Complete blood count | Mean values with Standard deviation | Electrolytes | Mean values with Standard deviation |
|----------------------|-------------------------------------|--------------|-------------------------------------|
| Hemoglobin (g/L)     | 8.67 ± 3.42                         | Sodium (mEq/L) | 135.23 ± 2.23                      |
| White blood count (X 10E9/L) | 13.23 ± 4.89                      | Potassium (mEq/L) | 3.39 ± 1.57                        |
| Platelets (X 10E9/L) | 265.31 ±127.16                      | Chloride (mEq/L) | 95.21 ± 3.81                       |
| C-reactive protein (mg/dl) | 6.21 ±5.65                         | Bicarbonate (mEq/L) | 22.45 ± 2.25                      |
| Blood Culture        | N=43 (%)                            | Sputum / Tracheal Culture | N=43 (%)                          |
| No growth            | 31 (72.09%)                         | No growth     | 11 (25.58%)                        |
| Staphylococcus aureus (MRSA) | 1 (2.32%)                        | Pseudomonas Aeruginosa | 12 (27.90%)                       |
| Staphylococcus aureus (MSSA) | 3 (6.97%)                         | Staphylococcus Aureus | 6 (13.95%)                        |
| Psuedomonas Aeruginosa | 5 (11.62%)                        | Klebsella Pneumonia | 3 (6.97%)                         |
| Escherichia Coli     | 1 (2.32%)                           | Steptococcus species | 3 (6.97%)                         |
| Streptococcus pneumonia | 1 (2.32%)                        | Haemophilus influenza | 2 (4.65%)                         |
| Burkholderia Cepacia | 1 (2.32%)                           | Burkholderia Cepacia | 2 (4.65%)                         |
| Stool for fat globules | N=43 (%)                          | Escherichia Coli | 2 (4.65%)                         |
| Positive             | 21 (48.83%)                         | Mixed Flora   | 1 (2.32%)                          |
| Negative             | 23 (51.16%)                         | Candida Species | 1 (2.32%)                         |
| Radiology features on X-ray Chest | N=43 (%)                   | Radiology features on HRCT Chest | N=43 (%)                       |
| Normal               | 1 (2.32%)                           | Normal        | 7 (16.27%)                         |
| Not performed        | 0                                   | Not performed | 4 (9.30%)                          |
| Consolidation        | 12 (27.90%)                         | Consolidation only | 5 (11.62%)                       |
| Hyperinflation       | 5 (11.62%)                          | Consolidation with hyperinflation | 4 (9.30%)                        |
| Prominent bronchovascular markings | 4 (9.30%)                        | Consolidation with collapse | 3 (6.97%)                         |
| Perihilar infiltrates | 2 (4.65%)                          | Consolidation, collapse and hyperinflation | 2 (4.65%)                        |
| Honey combing        | 19 (44.18%)                         | Bronchiectasis and hyperinflation | 18 (41.86%)                       |

MSSA=Methicillin Sensitive Staphylococcus Aureus, MRSA=Methicilin Resistant Staphylococcus Aureus, HRCT=High Resolution Computed Tomography.
50% patients with diarrhea and Steatorrhea. Five (11.62%) patients have hepatobiliary-pancreatic involvement during the course of disease. Around 86% patients presented with failure to thrive in our cohort. Faltering growth in these patients is consequence of dual action of pancreatic insufficiency leading to steatorrhea and utilization of calories due to poor pulmonary health. High resolution Computed tomography (HRCT) of chest showed 18 (42%) patients with some degree of bronchiectatic changes in our patients. Certain studies advocate CT scan as a tool to detect early pulmonary deterioration and showed that serial CT scans revealed early worsening whereas serial Pulmonary Function Tests (PFTs) performed at the same time remained unaffected or declined at a gentler rate in children with CF. About 28% patients in our data showed growth of pseudomonas aeruginosa in sputum cultures followed by Staphylococcus aureus. Staphylococcus aureus is usually the first microbe seen in CF patients in early part of their life followed by Pseudomonas aeruginosa. Colonization of pseudomonas in airways at the time diagnosis indicates late recognition of condition.

CONCLUSION

Respiratory presentations predominate in CF children followed by gastrointestinal features. Nearly half of our patient had bronchiectatic changes on CT scan chest and more than quarter had pseudomonas colonization in the airways at the time of diagnosis. There is significant delay in diagnosing patient with CF resulting in early deterioration of lung function, consequently affecting their growth and nutrition. Delta F-508 mutation was found to be uncommon in our study population. Hence, it is high time that the range and dissemination of CFTR mutations in Pakistani population should be determined by completely analyzing the CFTR gene in CF patients for prompt diagnosis and early management.

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REFERENCES

1. Zvereff VV, Faruki H, Edwards M, Friedman KJ. Cystic fibrosis carrier screening in a North American population. Genetics in Medicine. 2013;16(7):539-546. doi:10.1038/gim.2013.188

2. Ren C, Desai H, Platt M, Dixon M. Clinical outcomes in infants with cystic fibrosis transmembrane conductance regulator (CFTR) related metabolic syndrome. Pediatr Pulmonol. 2011;46(11):1079-1084. doi:10.1002/ppul.21475.

3. Bertrand CA, Frizzell RA. The role of regulated CFTR trafficking in epithelial secretion. Am J Physiol Cell Physiol. 2003;285(1):C1-C18. doi:10.1152/ajpcell.00554.2002.

4. Prasad R, Sharma H, Kaur G. Molecular Basis of Cystic Fibrosis Disease: An Indian Perspective. Indian J Clin Biochem. 2010;25(4):335-341. doi:10.1007/s12291-010-0091-1.

5. Shah U, Frossard P, Moattar T. Cystic fibrosis: defining a disease under-diagnosed in Pakistan. Trop Med Int Health. 2009;14(5):542-545. doi:10.1111/j.1365-3156.2009.02253.x.

6. Chang E Zabner J. Precision Genomic Medicine in Cystic Fibrosis. Clin Transl Sci. 2015;8(5):606-610. doi:10.1111/cts.12292.

7. Frossard PM, Girodon E, Dawson KP, Ghanein N, Plassa F, Lestringant GG, et al. Identification of cystic fibrosis mutations in the United Arab Emirates. Mutations in brief no. 133. Online Hum Mutat. 1998;1:412-413.

8. Kabra SK, Kabra M, Lodha R, Shastrti S, Ghosh M, Pandey RM, et al. Clinical profile and frequency of delta f508 mutation in Indian children with cystic fibrosis. Indian Pediatr. 2003;40(7):612-619.

9. El-Falaki M, Shahin W, El-Basha N, Ali A, Mehaney D, El-Attar M. Profile of cystic fibrosis in a single referral center in Egypt. J Adv Res. 2014;5(5):563-568. doi: 10.1016/j.jare.2013.07.005.

10. Ashraf M, Ahmed K, Chowdhary J, Rehana B, Ahmed J, Mir T. Clinical profile, diagnostic delay, and genetic make-up of cystic fibrosis in Kashmir, India. Lung India. 2011;28(2):97-100. doi:10.4103/0970-2123.80318.

11. Desgeorges M, Mégarbané A, Guittard C, Carles S, Loiselet J, Demaillé J, et al. Cystic fibrosis in Lebanon: distribution of CFTR mutations among Arab communities. Hum Genet. 1997;100(2):279-283. doi:10.1007/s004390050505.

12. Naguib M, Schrijver I, Gardner P, Pique SS, Zokry MA, et al. Cystic fibrosis detection in high-risk Egyptian children and CFTR mutation analysis. J Cyst Fibros. 2007;6(2):111-116. doi: 10.1016/j.jcf.2006.04.004.

13. Bhutta ZA, Moattar T, Shah U. Genetic analysis of cystic fibrosis in Pakistan: a preliminary report. J Pak Med Assoc. 2000;50(7):217-219.

14. Sawicka E, Zybert K. Meconium ileus in newborns with cystic fibrosis- results of treatment in the group of patients operated on in the years 2000-2014. Dev Period Med. 2015(1):32-40.

15. Mushtaq I, Wright VM, Drake DP, Mears MB, Wood CB. Meconium ileus secondary to cystic fibrosis The East London experience. Pediatr Surg Int. 1998;13(5-6):365-369.

16. Kintu B, Brightwell A. Episodic seasonal pseudo-Bartter syndrome in cystic fibrosis. Paediatr Respir Rev. 2014;15:19-21. doi: 10.1016/j.prrv.2014.04.015.

17. Ren C, Konstan M, Rosenfeld M, Pasta D, Millar S, Morgan W. Early childhood wheezing is associated with lower lung function in cystic fibrosis. Pediatr Pulmonol. 2013;48(8):745-750. doi:10.1002/ppul.22894.

18. London Jr NR, Reh DD. Differential Diagnosis of Chronic Rhinosinusitis with Nasal Polyps. In Rhinosinusitis with Nasal Polyps 2016(79):1-12. Karger Publishers.

19. Wells J, Farris R, Gosdin T, Dransfield MT, Wood ME, Bell SC, et al. Pulmonary artery enlargement and cystic fibrosis pulmonary exacerbations: a cohort study. Lancet Respir Med. 2016;4(8):636-645. doi:10.1016/s2213-2600(16)30105-9.
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20. Hayes D, Tobias J, Mansour H, Kirkby S, McCoy KS, Daniels CJ, et al. Pulmonary Hypertension in Cystic Fibrosis with Advanced Lung Disease. Am J Respir Crit Care Med. 2014;190(8):898-905. doi:10.1164/rcrm.201407-1382oc.

21. McCloskey M, Redmond A, Hill A, Elborn J. Clinical Features Associated with a Delayed Diagnosis of Cystic Fibrosis. Respiration. 2000;67(4):402-407. doi:10.1159/000029538.

22. Kawoosa MS, Bhat MA, Ali SW, Hafeez I, Shastri S. Clinical and mutation profile of children with cystic fibrosis in Jammu and Kashmir. Indian Pediatr. 2014;51(3):185.

23. Giglio L, Candusso M, D’orazio C, Mastella G, Faraguna D. Failure to thrive: the earliest feature of cystic fibrosis in infants diagnosed by neonatal screening. Acta Paediatrica. 1997;86(11):1162-1165.

24. de Jong PA, Lindblad A, Rubin L, Hop WC, de Jongste JC, Brink M, et al. Progression of lung disease on computed tomography and pulmonary function tests in children and adults with cystic fibrosis. Thorax. 2006;61(1):80-85.

25. Coffey MJ, Whitaker V, Gentin N, Junek R, Shalhoub C, Nightingale S et al. Differences in Outcomes between Early and Late Diagnosis of Cystic Fibrosis in the Newborn Screening Era. J pediatr. 2017;181:137-45. doi: 10.1016/j.jpeds.2016.10.043

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DAA and AGB: Conceptualized and jointly designed the study, and drafted the initial manuscript.

AQ and MK: Did the data collection, analysis and compiled the results.

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