Effect of malnutrition in infants with cystic fibrosis in India: An underestimated danger

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ABSTRACT

Aims: To assess the clinical profile and nutritional status of infants with cystic fibrosis (CF) and track their nutritional outcomes with treatment. **Materials and Methods:** This retrospective study was conducted in a tertiary-care institute in South India. Demographic and clinical information were collected. The nutritional status and treatment outcome was assessed by Z-scores for weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length (WLZ) at diagnosis and follow-up. **Results:** Nineteen infants with CF had mean follow-up duration of 9.7 ± 8.7 months. There was a mean delay of 2.9 ± 2.1 months from symptom onset to diagnosis, by which time infants were severely malnourished (mean WAZ -4.68 ± 1.8). Pneumonia, summer dehydration with electrolyte abnormalities (42.1%), and a combination of anemia, hypoalbuminemia, and malnutrition (42.1%) were the predominant features. Significant weight loss had been recorded in undiagnosed infants by second month of life before symptom onset. At follow-up, there was a remarkable improvement in WAZ (P 0.001), but not LAZ and WLZ. There was a high mortality rate of 37% in these infants. **Conclusions:** Malnutrition is a significant morbidity in infants with CF in India. There was significant improvement of WAZ with treatment, but it lagged behind the recommended targets. There is an opportunity for identification of CF infants at the time of vaccination at six and ten weeks of age, by the primary care physician and pediatrician. Screening of young infants having failure to thrive in the immunization clinic may be a strategy for early diagnosis of infants with severe CF phenotype.

Keywords: Cystic fibrosis, infant mortality, malnutrition

Introduction

Cystic Fibrosis (CF) is a genetic condition resulting from a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes for a chloride channel on the epithelial cells in various organs.[1] This defect causes dehydration of airway surface liquid in the lungs and obstruction of ducts in many organs due to viscid secretions.[2] Malnutrition and lung disease are the two main burdens of cystic fibrosis which is the commonest lethal genetic condition among Caucasians.[3,4]

Excessive chloride loss from the skin due to CFTR channel dysfunction in sweat ducts is the basis of high sweat chloride level, the diagnostic test for CF.[5] On hot days, infants are susceptible to dehydration and electrolyte imbalances due to this.

The etiology of malnutrition in CF is multifactorial and includes exocrine pancreatic insufficiency, inadequate calory intake due to lack of appetite, and high energy demand.[6] Infants and young children are particularly prone to severe malnutrition.[6] Long-term effects include stunting, poor cognitive function, and higher mortality.[7] The role of CF as a cause for infant mortality and malnutrition in India has not been investigated.

Malnutrition in CF sets in very early. It has been shown that even in developed countries, neonates screened positive for

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CF by newborn screening (NBS) develops growth retardation by the time diagnosis is confirmed by 3 weeks of age.[8] The challenge for a primary care physician in India is that there is neither NBS for CF in the country nor national guidelines to aid early identification of these infants.[9] Unless affected infants are diagnosed at the earliest, the therapeutic window for better nutrition is lost.[10] Once diagnosed, the strategies recommended to protect an infant with CF from malnutrition include complementary feeding with higher provision of energy (150–200%), micronutrient and salt supplementation, and pancreatic enzyme replacement therapy (PERT).[7]

Predictors of malnutrition in Indian children with CF have been described.[11] However, information on the nutritional recovery of infants from developing countries who are on CF treatment is lacking. The objectives of this study were to describe the early clinical manifestations of CF in infants, assess the response to nutritional therapy, and describe the challenges faced in nutritional management.

Materials and Methods

This was a retrospective review of medical records of infants diagnosed with CF in a tertiary-care institute in South India from January 2018 to June 2020 with the approval of the Institutional Review Board.

All subjects had diagnosis confirmed by either elevated sweat chloride levels (>60 mmol/L) or by identification of two pathogenic mutations of the CFTR gene. After diagnosis, each family had been educated about recommended nutritional intake and PERT as per the ESPEN-ESPGHAN-ECFS guidelines.[7] At each clinic visit, feeding issues were addressed by a dietitian and growth parameters monitored. Demographic and clinical data at presentation and documented growth parameters prior to diagnosis were collected from the database. Z-scores for weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length (WLZ) were calculated using "WHO Anthro" software.[12]

Statistical analysis

Descriptive statistics were reported using mean (standard deviation) and median (IQR). The trend over time for WAZ, LAZ, and WLZ was reported using Generalized Estimating Equation (GEE) and analysis was done using SPSS 21.0 software (IBM, Bangalore).

Results

Baseline data of 19 infants are shown in Table 1. All infants had developed symptoms by the time diagnosis was made at a mean age of 3 months. There was a significant drop in WAZ at diagnosis (*P* 0.001) compared to birth weight Z-score in all infants except in one baby who had treatment initiated at 3 weeks of age [Figure 1]. Failure to thrive (FTT) was documented as early as 6 weeks of age in 93% of untreated

Table 1: Demography, clinical and laboratory features at or prior to diagnosis of CF (*n*=19)

	n (%)
Demography	
Male gender	13 (68.4)
Born at term gestation	18 (94.7)
Mean birth weight, g	2760±420
Median age and IQR* at the onset of symptoms, months	1 (0.2, 2.5)
Median age and IQR at diagnosis, months	3 (3, 6)
Clinical features	
Oily stools/chronic diarrhea/recurrent diarrhea	4 (21.0)
Summer dehydration with electrolyte abnormalities	8 (42.1)
At least one episode of pneumonia	13 (68.4)
Edema/Anasarca	4 (21.0)
Neonatal jaundice (cholestasis)	1 (0.5)
Laboratory parameters	
Positive new-born screening (NBS)	1 (0.5)
Anemia (*n*=18)	13 (72.2)
Hypoalbuminemia (*n*=15)	12 (80.0)
Anemia+hypoalbuminemia without edema	8 (42.1)
Anemia+hypoalbuminemia + edema (triad)	4 (21.0)
Hypochloremic hypokalemic metabolic alkalosis	8 (42.1)
Sweat chloride (mmol/L) (*n*=15)	
->60	12 (80.0)
30-60	2 (13.3)
<30	1 (6.6)
Fecal elastase (μg/g of stool) (*n*=18)	
-<200	16 (88.8)
200-250	1 (5.5)
>250	1 (5.5)

*IQR: interquartile range
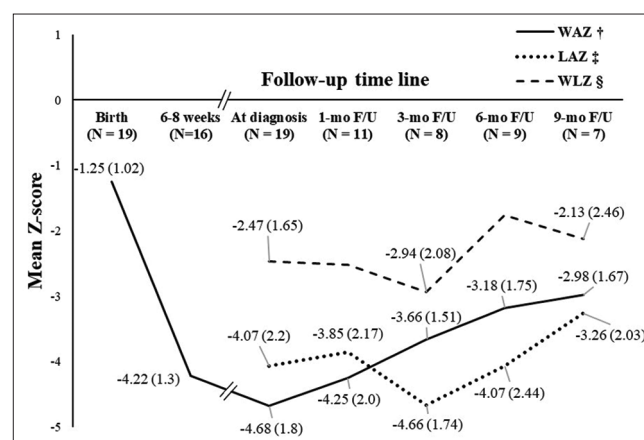
Figure 1: Anthropometry trend from birth, 6 weeks of age and up to 9-month follow-up (F/U) after diagnosis; *N = number of infants brought during each visit; † WAZ: weight-for-age Z-score; ‡ LAZ: length-for-age Z-score; § WLZ: weight-for-length Z-score

patients (*P* 0.001, N = 16). Pneumonia and summer dehydration with dyselectrolytemia (metabolic alkalosis, hypokalemia, and hyponatremia) were the predominant presenting features in these young babies. The mean delay to diagnosis after symptom onset was of 2.9 ± 2.1 months.

Seven (36.8%) infants died shortly after diagnosis due to pneumonia, sepsis, and/or malnutrition. The mean duration of

follow-up was 9.7 ± 8.7 months. Follow-up assessment at 1, 3, 6, and 9 months showed significant improvement of WAZ (P 0.001) with time. The average weight gain 3 months after initiation of treatment was 1650 ± 807 grams. However, LAZ and WLZ did not show statistically significant gains. The main challenges to optimal nutritional management were issues related to infant feeding (57%) and inability to sustain recommended PERT dose (21%). Intrafamilial conflicts related to the care of the sick child, feeding-related myths, and intercurrent illnesses were other factors.

Discussion

This study on infants with CF from a developing country provides important information on the magnitude of malnutrition and suboptimal response to treatment even after relatively early diagnosis in this cohort.

At diagnosis, 89% of the subjects had moderate to severe malnutrition, similar to data reported from other parts of India.[11] In contrast, multiple studies from developed countries have proved the positive impact of NBS on short- and long-term nutritional and overall outcomes.[13,14]

Anemia and hypoalbuminemia with or without edema have been recognized as a complication of severe malnutrition and presenting manifestation of CF.[15] This was a predominant presenting feature (42%) next only to pneumonia (68%) in this cohort.

Summer dehydration with characteristic electrolyte abnormalities was documented in a large number of these infants similar to reports from other countries.[16]

High mortality (37%), shortly after diagnosis, points to the critical level of malnutrition and morbidity which had set in by early infancy. None of the patients in this cohort had a history of meconium ileus (MI), a predominant reported cause of mortality in infants.[17] Early mortality associated with MI before confirmation of CF diagnosis might be the reason for this.

Clinical care of this cohort was supervised by a multidisciplinary team specially trained in CF care. Though significant improvement of WAZ was noted at follow-up, LAZ and WLZ gains were not significant. This is a matter of concern as optimal height/length gain in childhood correlates well with better pulmonary functions.[18] Both the mean WAZ and LAZ did not reach the target (-2 to +2) as recommended by CF guidelines.[7] It is noteworthy that the sole infant in this cohort identified during the neonatal period is the only one who maintained weight and length at 50th centile for age during the follow-up till two years of age. For optimal nutritional outcomes in infancy, attention to the unique challenges faced by CF families is necessary. Noncompliance to recommended treatment is a common problem worldwide.[19] In addition to the common feeding problems of infancy, recurrent hospitalizations, myths about

food items like milk and high-fat feed, and financial constraints were documented as barriers to adequate provision of nutrition and pancreatic supplements.

In developed countries, with the availability of highly effective CFTR modulators for treatment, clinical care of CF infants is provided by a highly specialized multidisciplinary team.[20] However, the significant role played by primary care physicians in the holistic management of CF patients from infancy through teenage is well appreciated.[21] Many countries in Asia, do not have a national strategy to ensure early diagnosis of CF as CF is presumed to be a very rare disease. The knowledge gap and need for extensive education regarding the early identification of patients with CF were well pointed in the recent publication from Saudi Arabia.[22]

In India, where nationwide NBS for CF is unlikely to be available immediately, sustainable methods for early recognition of CF are urgently needed. The primary care physicians are the first point of contact for most of these infants, especially when they are brought for immunization. Mandatory record of Z-score for weight in the vaccination record and identification of babies who are failing to thrive is absolutely essential. This in turn should trigger an evaluation strategy to look for potential causes including CF. Careful screening for additional clinical features like fat malabsorption and or respiratory infection can then be done. Simple blood tests to identify anemia, hypoalbuminemia, and alkalosis can further help to identify patients who need a referral to a specialist center for detailed evaluation. Cystic fibrosis should be considered in the differential diagnosis of young infants who present with anemia, hypoalbuminemia, or malnutrition when other causes are not evident.[15]

Conclusion

Malnutrition is a significant morbidity in infants with CF in India. When coupled with a late diagnosis there is a high risk of mortality. There was a significant improvement of anthropometric parameters with treatment, but these indices lagged way behind the recommended targets. Diagnosis of CF with severe phenotype may be made earlier if a comprehensive evaluation strategy is put in place at the national level for infants who have significant FTT at the time of six- and ten-week vaccination visits. Primary care physicians and community pediatricians have an important role in the early identification of CF and in providing continuity of care.

Key Messages

In infants with CF, significant malnutrition is evident as early as 6 weeks of age. Even though significant weight gain is possible with treatment, multiple challenges hinder achievement of target nutritional outcomes. Primary care physician has a pivotal role in identification and structured evaluation of infants who are failing to thrive at the time of vaccination visits. Initiation of appropriate treatment at the earliest is crucial for optimal growth, as well as for improved pulmonary functions.

References

1. Voter KZ, Ren CL. Diagnosis of cystic fibrosis. Clin Rev Allergy Immunol 2008;35:100-6.

2. Elborn JS. Cystic fibrosis. Lancet 2016;388:2519-31.

3. Slae M, Wilschanski M. Prevention of malnutrition in cystic fibrosis. Curr Opin Pulm Med 2019;25:674-9.

4. Kapnadak SG, Dimango E, Hadjiliadis D, Hempstead SE, Tallarico E, Pilewski JM, *et al.* Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease. J Cyst Fibros 2020;19:344-54.

5. Raina MA, Khan MS, Malik SA, Raina AH, Makhdoomi MJ, Bhat JI, *et al.* Assessment of correlation between sweat chloride levels and clinical features of cystic fibrosis patients. J Clin Diagn Res 2016;10:BC01-6.

6. Munck A, Boulkedid R, Weiss L, Foucaud P, Wizla-Derambure N, Reix P, *et al.* Nutritional status in the first 2 years of life in cystic fibrosis diagnosed by newborn screening. J Pediatr Gastroenterol Nutr 2018;67:123-30.

7. Turck D, Braegger CP, Colombo C, Declercq D, Morton A, Pancheva R, *et al.* ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. Clin Nutr 2016;35:557-77.

8. Patterson KD, Kyriacou T, Desai M, Carroll WD, Gilchrist FJ. Factors affecting the growth of infants diagnosed with cystic fibrosis by newborn screening. BMC Pediatr 2019;19:356.

9. Kumar P, Goyal JP. Positive newborn screening for cystic fibrosis, what to do next? Indian J Pediatr 2019;86:1147.

10. Sims EJ, Clark A, McCormick J, Mehta G, Connett G, Mehta A, *et al.* Cystic fibrosis diagnosed after 2 months of age leads to worse outcomes and requires more therapy. Pediatrics 2007;119:19-28.

11. Dhochak N, Jat KR, Sankar J, Lodha R, Kabra SK. Predictors of malnutrition in children with cystic fibrosis. Indian Pediatr 2019;56:825-30.

12. WHO | WHO Anthro Survey Analyser and other tools. WHO. World Health Organization. Available from: http://www.who.int/childgrowth/software/en/.

13. Pedersen MG, Højte C, Olesen HV, Pressler T, Skov M. Late diagnosis and poor nutrition in cystic fibrosis diagnosed before implementation of newborn screening. Acta Paediatr 2019;108:2241-5.

14. De Boeck K. Cystic fibrosis in the year 2020: A disease with a new face. Acta Paediatr 2020;109:893-9.

15. Kumar J, Chatterjee D, Lal SB, Kumar P. An Infant with Severe Anemia and Hypoalbuminemia. Indian Pediatr 2020;57:349-55.

16. Yalçın E, Kiper N, Doğru D, Özçelik U, Aslan AT. Clinical features and treatment approaches in cystic fibrosis with pseudo-Bartter syndrome. Ann Trop Paediatr 2005;25:119-24.

17. Parikh NS, Ibrahim S, Ahlawat R. Meconium Ileus. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021. Available from: http://www.ncbi.nlm.nih.gov/books/NBK537008/.

18. Mauch RM, Kmit AH, Marson FA de L, Levy CE, Barros-Filho A de A, Ribeiro JD. Association of growth and nutritional parameters with pulmonary function in cystic fibrosis: A literature review. Rev Paul Pediatr 2016;34:503-9.

19. Poulimeneas D, Grammatikopoulou MG, Devetzi P, Petrocheilou A, Kaditis AG, Papamitsou T, *et al.* Adherence to dietary recommendations, nutrient intake adequacy and diet quality among pediatric cystic fibrosis patients: Results from the GreeCF study. Nutrients 2020;12:3126.

20. Conway S, Balfour-Lynn IM, De Rijcke K, Drevinek P, Foweraker J, Havermans T, *et al.* European Cystic Fibrosis Society standards of care: Framework for the cystic fibrosis centre. J Cyst Fibros 2014;13(Suppl 1):S3-22.

21. Stern RC. The primary care physician and the patient with cystic fibrosis. J Pediatr 1989;114:31-6.

22. Asseri AA. Cystic fibrosis knowledge and practice among primary care physicians in southwest region, Saudi Arabia. J Family Med Prim Care 2020;9:1354-61.