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# ANAEMIA IN FAILURE AS A PRESENTING FEATURE OF CYSTIC FIBROSIS IN AN INFANT

Paediatric Medicine

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## ABSTRACT

**Background:** Cystic fibrosis (CF) is a multisystem genetic disorder of children and adults, inherited in an autosomal recessive pattern, affecting multiple organ systems in the body chiefly- Lungs, pancreas, intestines and others. In early infancy, anaemia may be the first clinical presentation of cystic fibrosis. This anaemia is often accompanied by hypoalbuminemia. Therefore, the concomitant presence of severe anaemia and hypoalbuminemia in early infancy should raise the possibility of CF. **Clinical Description:** We report a rare presentation of Cystic fibrosis (CF). Two-months-girl, presenting with complaint of passage of semisolid acholic stool for 3 weeks and paleness with pedal edema with failure to thrive (weight 3.2 kg). On examination, child had severe pallor, tachycardia, tachypnoea, hepatomegaly with just palpable spleen. On evaluation, child had severe anaemia with cholestasis, increased SGPT with hypoalbuminemia, deranged coagulation profile and hypothyroidism. Clinical exome sequencing was suggestive of Cystic Fibrosis. **Management & Outcome** Child was transfused with blood products (Packed red cells) and was started on supportive care for nutrition and supplements were started. Thyroxine replacement therapy was started. Unfortunately, child succumbed to aspiration pneumonia. **Conclusion:** Severe anemia can be the first and presenting symptom of cystic fibrosis, often accompanied by hypoalbuminemia. It may precede respiratory or gastrointestinal symptoms of cystic fibrosis by many months. Neonatal/infantile cholestasis although rare is the earliest manifestation of liver involvement in CF. Multidisciplinary approach to maximize long term survival.

## KEYWORDS

cystic fibrosis, cholestasis, hypoalbuminemia, Severe anemia

## INTRODUCTION

Cystic fibrosis (CF) is a multisystem genetic disorder of children and adults, inherited in an autosomal recessive pattern, caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator gene (CFTR gene or CF gene) on the long arm of chromosome 7, affecting multiple organ systems in the body chiefly- Lungs, pancreas, intestines and others. [1] The most common variant (70% mutation) is F508del resulting from deletion of three nucleotides that leads to a loss of a single phenylalanine residue at codon 508. [2] Normally, the CF gene codes for the CFTR protein (member of the ATP binding cassette superfamily of proteins) which is expressed largely in the epithelial cell of airways, gastrointestinal tract (including pancreas and biliary system), the sweat glands and the genitourinary system. The CFTR protein functions as a chloride channel. The dysfunctional CFTR protein (mutated) causes impaired secretion of these anions-chloride, thiocyanate, bicarbonate, glutathione and massive absorption of sodium and water which makes the airway secretions thick, viscous and dehydrated and a vicious cycle of infection and inflammation continue. [3]

In early infancy, anaemia may be the first clinical presentation of cystic fibrosis. [4] This anaemia is often accompanied by hypoalbuminemia. [5] These two manifestations can precede respiratory symptoms for many months. Therefore, the concomitant presence of severe anaemia and hypoalbuminemia in early infancy should raise the possibility of CF. Hereby we report a rare presentation of cystic fibrosis as severe anemia with hypoalbuminemia.

### Clinical Description

A two months old girl, second by birth order, born out of non-consanguineous marriage, presented with severe anaemia, progressive swelling of hands and feet, passage of semisolid pale stool (Stool colour card-3) since 3 weeks. No history of jaundice, high coloured urine, bleeding tendency, lethargy, poor feeding, irritability or seizures. Child was born late preterm (36 weeks) by normal vaginal delivery, birth weight of 2.4 kg. There was also maternal history of gestational hypertension (given labetalol) and hypothyroidism (On thyroxine). No other significant problems, passed meconium within first 24 hrs. Age-appropriate development and immunization.

On examination, child had severe tachycardia, tachypnoea, severe pallor with pedal edema (Pitting) with failure to thrive ( table 1), no Jaundice and no stigmata of acute liver cell failure. Abdomen was distended with moderate hepatomegaly (6 cm below right subcostal margin, soft, nontender, well-defined borders, liver span: 8cm) and a just palpable spleen. Respiratory system, Cardiovascular system and Central nervous system examination was unremarkable. Fundus examination didn't show any chorioretinitis or cherry red spot.

Investigations (Table 2) revealed child had severe anaemia with conjugated hyperbilirubinemia, increased SGPT with deranged synthetic functions of liver (Hypoalbuminemia, Coagulopathy: prolonged PT and APTT) with persistent hyponatremia. Serum TSH was increased to 10 µIU/Ml

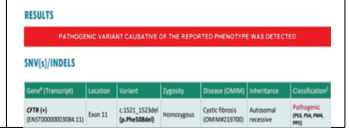
Provisional diagnosis was severe anaemia in failure with Cholestasis and Failure to thrive with deranged synthetic functions of liver (hypoalbuminemia with coagulopathy). Child was being worked up for cholestasis, mainly Galactosemia and Glycogen Storage disease (GSD).

Clinical exome sequencing was sent considering multisystemic disease which confirmed diagnosis of Cystic Fibrosis (CFTR+; Phe508del)

**Table 1: Anthropometry of Child**

| ANTHROPOMETRY | Values | SD scores |
|---|---|---|
| Weight | 2.9 kg | Less than -3 SD |
| Length | 52.5 cm | Less than -2 SD |
| Head circumference | 36.5 cm | Between -2 SD to -1 SD |
| Weight for Length | | Less than -3SD |
| Impression | Failure to Thrive | |

**Table 2: Investigations**

| Complete Hemogram | Day of admission-1 | Day of admission-3 | Day of admission-6 |
|---|---|---|---|
| Hemoglobin (gm/dl) | 4.9 | 5.6 | 6.4 |
| RBC count (million/mm3) | 1.6 | 2.2 | 3.24 |
| TLC (/mm3) | 15,800 | 13,300 | 14,600 |
| Hematocrit (%) | 16.5 | 19.7 | 18.6 |
| Platelet count (lacs/mm3) | 3.28 | 3.46 | 4.22 |
| RDW-CV (SD) | 20.2% | 19.6% | 19.2% |
| MCV (fL) | 98.5 | 96 | 100 |
| MCH (pg/dL) | 28 | 30 | 26.8 |
| MCHC (%) | 29.6 | 28.4 | 34.4 |
| Reticulocyte count | 5% | | |
| Corrected reticulocyte count | 2.2% | | |
| ESR (mm/hr) | 110 | | |
| Peripheral smear | Mainly normocytic normochromic with few macrocytes. Mild polychromasia seen. | | |
| Liver function test | | | |
| Total Serum Bilirubin (≤2 mg/dL) | 4.8 | 3.6 | 2.1 |
| Direct bilirubin (mg/dL) | 1.9 | 1.2 | 0.8 |
| SGOT (0-40 U/L) | 126 | 84 | 46 |
| SGPT (0-40 U/L) | 44 | 40 | 38 |
| Alkaline phosphatase (54-141 U/L) | 504 | 326 | 296 |
| Total protein (6.4-8.3 g/dL) | 3.58 | 4.2 | 4.6 |
| Albumin (3.5-5.2 g/dL) | 1.6 | 2.1 | 2.6 |
| Globulin (2.9-3.1 g/dL) | 1.98 | 2.3 | 2.7 |
| GGT(U/L) | 8.2 | | |
| BUN (mg/dL) | 4 | | |
| Creatinine | 0.5 | | |
| Serum Triglyceride (mg/dL) | 102 | | |
| LDL cholesterol (mg/dL) | 35 | | |
| HDL cholesterol (mg/dL) | 58 | | |
| Total cholesterol (mg/dL) | 96 | | |
| Serum Na+ (136-145 mEq/L) | 126 | 122 | 123 |
| K+( 3.5-5mEq/L) | 4.6 | | |
| Random blood sugar (mg/dL) | 96 | | |
| Bleeding profile | Day of admission-1 | Day of admission-3 | Day of admission-6 |
| Prothrombin time (PT) (Seconds) | T max | 24 | 14 |
| International Normalized Ratio (INR) | - | 1.87 | 1.2 |
| Partial Thromboplastin Time (PTT) (seconds) | V≥V max | | |
| Thrombin Time (TT) (Seconds) | T max | | |
| Plasma Fibrinogen (mg/dL) | ≤ 0.80 | | |
| Iron profile | | | |
| Serum Iron (60-170 mcg/dL) | 112 mcg/dL | | |
| TIBC (240-450 mcg/dL) | 131 mcg/dL | | |
| Serum Ferritin (7-140 ng/mL) | 468 | | |
| Thyroid profile | | | |
| Free T3 (2.15-5.83 pg./mL) | 1.48 pg./mL | | |
| Free T4 (0.92-1.99 ng/dL) | 1.06 ng/dL | | |
| TSH (0.73-8.35microIU /mL) | 10.8microIU/mL | | |
| Ultrasonography Abdomen | Normal liver echogenicity,<br>Gall Bladder contour is normal.<br>Contractility index: 0.5,<br>CBD not well visualized.<br>No evidence of Biliary atresia, cysts, intra hepatic biliary radicle dilatation,<br>Moderate hepatomegaly present | | |
| Ultrasonography skull | No intracranial calcifications. Grade 1 germinal matrix haemorrhage. | | |
| Clinical exome sequencing | CFTR+, exon 11, Variant: p.Phe508del, Homozygous, Autosomal recessive, Pathogenic.  | | |



**Managements and Outcome**

Child was managed conservatively with Nutritional support, Supplementation of Fat-soluble vitamins (Cholestatic doses), packed red cell transfusion, intravenous antibiotics. Choleretic therapy with ursodeoxycholic acid was initiated. Thyroxine replacement therapy was started. Unfortunately, child succumbed to aspiration pneumonia

**Discussion and Review of Literature:**

The primary analysis of our case suggested a multi-system disease with predominant hepatic involvement with severe anaemia and failure to thrive. There are many causes of isolated hepatomegaly with the above findings-Intrauterine infections (TORCH) and metabolic/storage disorder. The possible storage /metabolic disorder can be Glycogen storage disorder (GSD), Lipid storage disorder (Gaucher and Niemann-Pick disease), iron storage (Neonatal hemochromatosis due to gestational alloimmune liver disease: GALD), galactosemia, cystic fibrosis.

Galactosemia was a strong possibility in the presence of jaundice, hepatomegaly, coagulopathy, severe anaemia and the child had been started on a lactose free milk initially. However, there was no hypoglycemia or any features of sepsis, cataract. Urine for NGRS (Non glucose reducing substances) was negative. However, we couldn't send GALT assay since the child had already received PRBC transfusion.

Cystic fibrosis-associated liver disease (CFLD) can present in early infancy with features of hepatomegaly, cholestasis, transaminitis, dyslipidemia and severe anaemia along with hypoalbuminemia. Severe anaemia can be the first sign of cystic fibrosis in 7-10% infants with CF and the concomitant presence of severe hypoalbuminemia makes it more likely. [4] Nearly all of the above features are being displayed by the index case. The index case further has persistent hyponatremia thus contributing more to the diagnosis of CF (Persistent hyponatremic, hypochloremic metabolic alkalosis). However, the presence of normal liver echotexture is not consistent with CF, but it could come over the course of illness.

Pulmonary complications are the predominant cause of mortality and morbidity in CF. CFLD is an evolving paradigm and is believed to be the third commonest cause of mortality in patients with CF. [7] The symptoms evolve over time, and in early infancy anaemia, often accompanied with hypoalbuminemia may be the first clinical presentation of CF. [4, 5] These infants typically have normocytic, normochromic anaemia secondary to multiple factors. CF patients especially those with pancreatic insufficiency (more incidence of CFLD) have deficiency of fat-soluble vitamins (especially Vitamin E) which can cause anaemia associated with hemolysis due to erythrocyte fragility. Vitamin K deficiency causes prolonged PT/INR which in turn can cause Vitamin K deficiency related microbleed and thus again contributing more to the anaemia. Also, CF patient with anaemia and hypoalbuminemia have ineffective erythropoiesis (due to protein energy malnutrition). There is impaired proliferation of erythroid precursors and egress of erythroid components from bone marrow. [8] Both vitamin E and A deficiency also contribute to this ineffective erythropoiesis. [9,10] Furthermore hepcidin-related anaemia is more commonly the leading cause of anaemia in older CF patients especially with pulmonary complications. [11] Also, piperacillin-induced severe hemolytic anaemia has been reported in CF patients. (Piperacillin is a common antipseudomonal antibiotic, which can be used in CF.) [12, 13, 14] But in our case, we have not used piperacillin as the antibiotic.

To establish the diagnosis of CF, sweat chloride estimation is the first step to be done, followed by CFTR genetic analysis, and CFTR physiologic tests. All individuals diagnosed with CF should have a sweat test and a CFTR genetic analysis performed. [6] However, in neonates and early infancy, the sweat chloride test is difficult to perform due to logistic issues; therefore, the reliance is more towards the genetic analysis (CFTR mutation panel). F508del is the commonest CFTR gene mutation in western world (80% of all tested

alleles). However, this mutation is less commonly observed in Asian and Indian settings, therefore we need complete CF gene sequencing for confirmation of diagnosis. [15,16]

Sismanlar et al., 2016 did a similar study on CF children to determine the factors associated with early severe anaemia in them. The study included 231 infants with CF from 3 paediatric CF centres ten-year period that were retrospectively reviewed in terms of severe anaemia as the first sign of CF. Severe anaemia as the first sign of CF was noted in 17 of 231 patients. [4]

Another data from a case report by Kumar et al.2020, reported a 2 months old girl child who presented with similar features anaemia, anasarca, pale stools, chubby cheeks, failure to thrive, microcephaly, moderate hepatomegaly, transaminitis, cholestatic jaundice). Their close differentials were between citrin deficiency ad CF. However, the child succumbed to severe sepsis and died. Post mortem histopathology of Lungs, liver and heart revealed features consistent with CF. Genetic studies were also done with peripheral blood collected at autopsy which revealed CFTR gene mutation (WT/F508del) [17]

Our case highlights the importance of severe anaemia, with hypoalbuminemia as the first sign of CF. Neonatal/infantile cholestasis, although rare (≤ 2%) is the earliest manifestation of liver involvement in CF. [18] It is a direct consequence of the basic CFTR defect resulting in obstruction of extrahepatic bile ducts ( "Inspissated Bile syndrome"). Hence, it is important to rule out other common causes of neonatal cholestasis like biliary atresia and also to consider the diagnosis of CF in infants who present with cholestasis.

## CONCLUSION

Severe anemia can be the first and presenting symptom of cystic fibrosis, often accompanied by hypoalbuminemia. It may precede respiratory or gastrointestinal symptoms of cystic fibrosis by many months. High index of suspicion in patients with severe anemia and hypoalbuminemia should prompt genetic testing for definitive diagnosis of cystic fibrosis. Neonatal/infantile cholestasis although rare is the earliest manifestation of liver involvement in CF. Multidisciplinary approach to maximize long term survival.

### Lessons Learnt :

1. An infant presenting with severe anaemia, often accompanied with hypoalbuminemia needs to be evaluated extensively and CF to be kept as one of the close differentials.
2. Neonatal/infantile cholestasis although rare is the earliest manifestation of liver involvement in CF.
3. Importance of genetic testing in the diagnosis of CF especially in neonates and in early infancy.
4. Multidisciplinary approach to maximize long term survival.

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