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**Author/s:**

Bolia, R;Hardikar, W;Robinson, P

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No Sweat, No Genes: A Diagnostic dilemma

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Rishi Bolia<sup>1</sup>, Winita Hardikar<sup>1</sup>, Phil Robinson<sup>2</sup>

Department of Gastroenterology<sup>1</sup> and Respiratory Medicine<sup>2</sup>, The Royal Children's hospital,  
Melbourne

**Name and addresses (postal and e-mail) of the corresponding author**

Dr Rishi Bolia

Department of Gastroenterology

Royal Children's Hospital Melbourne

Ph. 613 93455060

Fax 613 93456240

E-mail – [rishi.bolia@rch.org.au](mailto:rishi.bolia@rch.org.au)

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## Case report

A 2 ½ month old girl presented to the emergency department with three days of cough and coryza, with a mildly increased work of breathing. She had failure to thrive and weighed 3190 g. (Z score = - 3.72). The weight for length Z score was - 3.11, which suggested severe acute malnutrition. She had a birth weight of 2570 g. (Z = -1.55), but had been dropping centiles since she was 1 month old. The child had been exclusively breast fed for the initial 2 months of life and had been commenced on formula top – ups 15 days prior to coming to our centre without improvement. She was born at 38 weeks' gestation by a normal vaginal delivery. The antenatal period was uneventful, apart from her mother having gestational diabetes mellitus. She had an older female sibling who was two years old and was well and healthy. Her parents were Somalian and there was no consanguinity. There was no history of any chronic illness in the family. On examination, she was alert but pale looking on general appearance. She had pitting oedema in both lower limbs. She was found to have mild intercostal and subcostal recessions. Chest was clear on auscultation, with equal air entry bilaterally. Her abdomen was soft on palpation and her liver was palpable 5 cms below the costal margin. There was no splenomegaly. She was admitted for evaluation. Her initial blood investigations showed microcytic anaemia, hypoalbuminemia and deranged liver function tests in the form of an elevated ALT and GGT. (Table 1). Chest X-ray showed some peri hilar and peri bronchial thickening bilaterally but no focal collapse or consolidation. An ultrasound scan of her abdomen showed a diffusely enlarged echogenic liver with a rounded contour but no focal lesion or intrahepatic biliary dilatation. Stool examination showed +++ fat globules. Albumin and blood were given by infusion and she was started on a high medium chain triglyceride containing formula. Pedal oedema subsided. Initial possibilities of a TORCH infection, Cystic Fibrosis, Schwachmann-Diamond syndrome and lysosomal storage disorders were considered and appropriate investigations were sent. A sweat chloride estimation was attempted but was unsuccessful. The standard and extended genetic panel (38 genes) for cystic fibrosis mutations was sent but was negative. She started gaining weight. After ten days of inpatient stay she was discharged at a weight of 3.43 kg. (Z = - 4.50), with a plan for outpatient follow up in a week.

She presented to the emergency department 4 days after discharge, with fever and tachypnoea. She was desaturating with saturations of 84-87%. Her chest x- ray showed peri hilar infiltrates. Her blood and urine culture grew *Escherichia coli*. She was treated with intravenous ampicillin and gentamicin and co-trimoxazole. As a result of persistence of

respiratory symptoms a broncho–alveolar lavage was performed, which showed *Pneumocystis jirovecii*. She improved with intravenous co – trimoxazole therapy. At this admission, her albumin and haemoglobin levels had dropped again and further albumin and blood was transfused. She was then also commenced on fat soluble vitamins, pancreatic enzyme replacement therapy as her faecal elastase was found to be low ( $< 15$ , normal  $> 200$   $\mu\text{g/g}$ ). Sweat chloride was attempted again, but adequate sweat could not be collected. Her Immunoreactive trypsinogen (IRT) value from her newborn screen was traced and was found to be high at 1087 ng/ml. (Normal  $< 300$ ) but as she did not have one of the 12 CFTR gene mutations included in the subsequent screening panel her newborn screen had been reported as negative. She was also evaluated for a primary immunodeficiency tests for Immunoglobulins and T and B cell subsets which were normal. Bone marrow examination was normal. A liver biopsy showed moderate chronic inflammation in the portal tracts. TORCH profile, Urinary metabolic screen, transferrin isoforms and amino – acid profile was negative. A duodenal biopsy showed mucus plugs in the duodenum suggestive of cystic fibrosis. At 5 months of age a repeat sweat chloride was attempted, and finally an adequate amount of sweat was collected, which showed a high chloride levels (107 mmol/L, Normal  $< 40$  mmol/L) confirming the diagnosis of CF. She was taken under the care of the CF team at the hospital and now with appropriate care and management has been doing well. She is now 17 months old and weighs 10 kg. ( $Z = 0.07$ ).

## Discussion

We report a very unusual presentation of cystic fibrosis. While suspected clinically, the diagnosis was difficult to confirm due to the inability to obtain sweat chloride and the ethnicity of the patient who had none of the extended panel of CF genes identified. Traditionally it was believed that CF only affects Caucasians. (1) However, in recent years there have been reports of CF from other ethnicities, including Africans. (1) Anaemia, hypoproteinaemia and failure to thrive were the presenting features in this child. This presentation occurs in only 5% of all children with CF (2) Previous studies describe the anaemia in CF as haemolytic, as a result of deficiency of fat-soluble vitamin E, which acts as a protective antioxidant. (3) In our patient we found that the vitamin E levels were low, and there was no further drop in haemoglobin once we started her on vitamin E supplementation, thus confirming the hypothesis. The precise aetiology of hypoproteinaemia is not clear. Liver dysfunction is unlikely to be the cause as the biopsy was near normal. It has been established that there is no leakage of protein into the gut in CF (4). Our patient presented with protein –

energy malnutrition (PEM). Initiation of pancreatic enzymes and a high calorie formula led to an improvement and she started gaining weight. Characteristic changes on the duodenal biopsy i.e. inspissated eosinophilic mucin within crypts (5) gave us an objective pointer towards the diagnosis, which was finally confirmed when the sweat chloride was repeated for a third time.

Pneumocystis pneumonia (PCP) is reported mainly in immunocompromised children and has been rarely reported in children with CF (6). Our patient was found to have *P. jirovecii*. As symptoms improved only after treatment for it was started, it suggests a causal role for *P.jirovecii* rather than colonization/contamination.

This girl was born in Australia and had been screened for CF in the new born period. In the state of Victoria screening comprises a two-step process with all specimens assayed for Immunoreactive trypsinogen (IRT) and the top 1% of results proceeding to a mutation analysis of the 12 commonest mutations seen in the Victorian community. This has been found to have a sensitivity of 95.8 % (7). Our patient was reported as negative on the newborn screen even though she had a high IRT as she did not have one of the mutations on the screening panel and it highlights the need for additional screening in non – Caucasian patients with a possible extended mutation screening, repeat IRT or a sweat chloride test. We could not determine the causative mutation in our extended 38 gene panel, which is not surprising as mutations for CF are often population-specific and each country needs to determine the mutations present among its people and tailor the genetic diagnostic tools accordingly. Africa is lagging in this regard, with 78% of countries having no published record of any molecular investigation of CF. (1)

To conclude, we report an infant of African origin who had failure to thrive, anaemia, hypoprotienemia and PCP as presenting features of cystic fibrosis. In patients who present with these constellation of symptoms CF should always be considered as a differential diagnosis even when the newborn screening is negative.

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**Multiple choice questions:**

1. Although CF is often thought of as a respiratory disease, physicians should also suspect CF in infants with unexplained –
  - A. Growth retardation
  - B. Anaemia
  - C. Steatorrhea and Fat soluble vitamin deficiency
  - D. Dehydration and electrolyte disturbances
  - E. All of the above

The answer is E Growth retardation is an early and prominent feature of CF. It may precede respiratory symptoms. 4-5% of children with CF may initially present with severe anaemia. It is multifactorial and may occur as a result of iron deficiency, inflammation or haemolysis (Vitamin E deficiency). Exocrine pancreatic insufficiency manifests as steatorrhea and fat soluble vitamin deficiency. Dehydration and hyponatremic, hypochloremic metabolic alkalosis (Pseudo Barter's Syndrome ) is one of CF the rare complications, especially in

infants and young children in situations accompanied by increased sweating and/or other causes of additional loss of sodium and chlorine

2. In newborn screening for cystic fibrosis, which of the following is not true -

- A. The newborn screening for CF is a tiered approach, with Immunoreactive trypsinogen (IRT) as the first step.
- B. IRT is measured on a newborn faecal sample
- C. Newborn screening protocols that use DNA analysis for CF causing mutations also detect carriers.
- D. Children detected to have CF on newborn screening have better long term outcomes
- E. It is a cost – effective public health strategy

The answer is B All cystic fibrosis newborn screening protocols measure Immunoreactive trypsinogen in the first week of life as the initial step. However, a wide range of approaches are subsequently used to improve the positive predictive value. IRT is measured on a dried blood spot. DNA analysis for cystic fibrosis – causing mutations also detect carriers, which is considered undesirable for a NBS program. Newborn screening prevents severe malnutrition and improves long-term growth and cognitive function. Cost of care of patients with cystic fibrosis is substantially lower if the disease is detected through early screening.

3. All of the following confirm a diagnosis of cystic fibrosis except –

- A. A history of CF in a sibling plus abnormal sweat chloride concentration
- B. Identification of a CF disease-causing mutation in each copy of the CFTR gene (i.e., on each chromosome
- C. Characteristic clinical features plus abnormal nasal potential difference
- D. A positive immunoreactive trypsinogen test
- E. Meconium ileus plus abnormal sweat chloride concentration

The answer is D The Cystic Fibrosis Foundation panel’s consensus is that the diagnosis of CF should be based on the presence of 1 or more characteristic clinical features, a history of CF in a sibling, or a positive newborn screening (NBS) test, plus laboratory evidence of an abnormality in the CF transmembrane conductance regulator (CFTR) gene or protein in the

form of an abnormal sweat chloride concentration or nasal potential difference or identification of a CF disease causing mutation in each copy of the CFTR gene (i.e., on each chromosome). A positive IRT by itself is not confirmatory.

### **Learning points**

1. Cystic fibrosis may present with failure to thrive, severe anaemia, oedema and hypoproteinemia in an infant.
2. A negative newborn screen should not preclude the diagnosis of Cystic Fibrosis
3. *Pneumocystis Jirovecii* is an unusual pathogen in CF but should be considered in children with persistent respiratory symptoms.