Severe CF manifestation with anaemia and failure to thrive in a 394delTT homozygous patient

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Abstract

We report on a 394delTT homozygous cystic fibrosis (CF) patient with severe disease progression. At the diagnosis made at the age of 2.5 months, he suffered from macrocytic anaemia as the most prominent symptom of CF, malnutrition, hypoproteinaemia and profound hypoalbuminaemia, but demonstrated only minimal pulmonary symptoms. Abnormal sweat chlorides confirmed the diagnosis of CF. Severe pulmonary and liver disease caused death after 6 years.

1. Introduction

In most patients with cystic fibrosis (CF), pulmonary symptoms initially prevail [1]. Another predominant feature is maldigestion that frequently begins in early childhood. Pancreatic exocrine dysfunction causes maldigestion characterised by failure to thrive, diarrhoea, hypoproteinaemia, oedema and anaemia. Severe anaemia as the initial manifestation was described rarely [2,3]. Prospectively, the frequency of clinically significant anaemia has been estimated to develop in 4% of CF infants [4].

The frameshift mutation 394delTT, which is very rare among CF chromosomes worldwide, was found to be a relatively common cause of CF in Northern European countries [5–7]. In Estonia, this mutation ranks as the second most common CF alteration, accounting for 13.3% of CF chromosomes [8].

We describe a male patient with severe anaemia at diagnosis, who developed chronic pulmonary disease at 1 year of age, liver cirrhosis at the age of 4 years and despite aggressive treatment died of cardiopulmonary deficiency at the age of 6 years.

2. Case report

A 1-month-old entirely breastfed boy was admitted to the local hospital due to failure to thrive and frequent dark green stools. He was born at term with a birth weight of 3000 g. Weight at hospitalisation was 2900 g. His hemogram was normal (haemoglobin 140 g/l, red blood cells \(4.4 \times 10^12\)), due to probable maldigestion (loose stools with undigested food particles), the infant was treated for 10 days with pancreatic enzyme supplements. Formula milk was added to his diet. He gained 250 g in 10 days and was discharged.

Further weight gain remained poor, and at the age of 2.5 months he was readmitted with malnutrition (weight 3430 g – 4 S.D., length 55 cm – 2.5 S.D.) and severe anaemia (haemoglobin 65 g/l, RBC \(4.4 \times 10^{12}\), hematocrit 0.22), initially to the local hospital and then to the University Hospital due to persistent anaemia. The routine laboratory workup demonstrated anisopoikilocytosis and polychromasia in the peripheral blood smear; macrocytoses with mean corpuscular volume 126
fl, (normal 84–105 fl), mean corpuscular haemoglobin 37 pg (normal 27–34 pg), reticulocytes 3.1%, thrombocytopaenia 99×10⁹. Serum total protein and albumin concentrations were low, 40 g/l and 23 g/l, respectively. Unconjugated bilirubin, serum iron, an indirect and direct Coombs test, a Price–Jones curve and bone marrow smear were all normal. The patient has neither hepato–or splenomegaly nor other signs of hemolysis. He had not passed any visible blood, and several tests for faecal haemoglobin were negative. Nevertheless, the mother reported an infrequent cough and a salty-tasting kiss. The chest radiograph demonstrated minimal changes with left-side lobular overaeration, but no sign of pneumonia. Abnormal sweat chlorides (105–119 mmol/l) confirmed the diagnosis of CF.

The infant was treated with albumin and glucose infusions, antibiotics, pancreatic enzymes and water-soluble vitamins (C, B₁₂, B₆ and folate). As anaemia continued, he was transfused with packed red blood cells. After confirmation of the CF diagnosis, liposoluble vitamins A (4000 IU/day), D (500 IU/day) and E (6 mg/day) were added. The patient was discharged after 20 days with a weight of 3850 g and normalised blood count (haemoglobin 122 g/l, RBC 3.6×10¹²)

The infant later showed severe disease manifestation, and was readmitted at the age of 4 months with bilateral pneumonia (Staphylococcus aureus). Altogether, during the first year of life he was hospitalised in the CF Centre seven times due to pulmonary exacerbations. His weight gain was still poor, although dietary intake was calculated at between 130–150% of the required values for his age.

The illness progressed rapidly. The first Pseudomonas aeruginosa positive sputum was found at 6 months of age, and chronic colonisation developed approximately 1 year later. Chronic pulmonary disease with left-side atelectasis and persistent diffuse changes characteristic of CF were diagnosed from 10 months of age, and severe cardiopulmonary deficiency at 2 years 9 months. Liver disease developed quickly. Liver enzymes increased significantly after 3 years of age, and by the age of 4.5 years liver cirrhosis with signs of portal hypertension developed. Although the patient was hospitalised 21 times at the CF centre, mostly due to pulmonary exacerbations, the boy died at the age of 6 years.

Molecular analysis of the CFTR gene revealed mutation 394delTT in both alleles. His parents were of Estonian ancestry and were non-consanguineous over at least five generations. Haplotype analysis was performed using two extragenic (XV2c, KM19) and four intragenic polymorphic sites (IVS8CA, IVS17BTA, IVS17BCA, IVS5T/7T/9T) [8] and interestingly, different haplotypes were found. Paternal mutation has been linked with microsatellite haplotype B/23/36/13-9T, exclusively associated with the 394delTT mutation in Finland [5], and the maternal alteration has been connected with the B/25/36/13-9T haplotype found only in the Estonian population.

3. Discussion

In this anaemia patient, malnutrition and hypoalbuninaemia were the most prominent symptoms, when CF was diagnosed at the age of 2.5 months. Overall, the pathogenesis of early anaemia in CF has not been conclusively established. Most previous studies describe the anaemia as haemolytic, implicating the malabsorption of fat-soluble vitamin E [4,9–11], which appears to act as a protective antioxidant toward peroxidation of membranous polyunsaturated fatty acids [12]. It has also been shown, however, that vitamin E deficiency in CF patients is irrespective of pancreatic function, body weight, and even the administration of pancreatic enzymes and liposoluble vitamins [13]. Among infants newly diagnosed with CF, the frequency of vitamin E deficiency has been found to be very high, ranging from 38 to 59% [14,15]. Interestingly, only approximately 4% of these children develop clinically significant anaemia [3,4], suggesting that additional/modifying factors most likely contribute to the manifestation of severe anaemia in CF patients. Although in our patient, the only intimation of haemolysis was mild reticulocytosis and other features did not contribute to typical haemolytic anaemia, due to lack of the data we could not rule out the importance of vitamin E deficiency in the initiation of anaemia. Although after the diagnosis of CF, vitamin E was supplemented in low levels according to present guidelines, signs of haemolytic anaemia did not reoccur.

The slightly hypercromic macrocytosis detected is harder to explain. One reason could be a deficiency of folic acid due to malabsorption, or increased folate utilisation by rapidly-proliferating bone marrow in chronic haemolytic anaemia, or a combination of both. Although anaemia in our patient was not prolonged, persistent malnutrition plausibly contributed to the manifestation of anaemia.

Our 394delTT homozygous patient showed extraordinarily complicated disease manifestation, although CF was diagnosed at an early age and aggressive treatment was provided at the CF Centre. This finding corresponded with the severe disease manifestation with high sweat chlorides, pancreatic insufficiency, and high rate of liver disease described in a group of Swedish 394delTT patients [7].

The severe manifestation of the disease correlates with the prediction from the character of the mutation. Due to the deletion in exon 3, stop codon is generated in exon 4 and truncated protein is synthesised. In consequence, no functional CFTR protein is expected at the apical membrane of the epithelial cells in patients homozygous for the 394delTT mutation [16]. In a recent
study, no CFTR activity could be demonstrated with nasal epithelial cells derived from 394delTT/F508del compound heterozygous patients [17].

4. Conclusion

According to the predicted molecular character of 394delTT mutation, our homozygous patient showed severe disease manifestation. In rare cases of CF, anaemia may be the leading symptom present together with malnutrition, and should always be considered in the differential diagnosis of anaemia. More investigations are needed to clarify the mechanisms of early anaemia in CF and to assess the possible poor prognostic value of clinically significant anaemia in CF babies.

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References