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Cystic fibrosis in premature infants

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Abstract

There are few reports of cystic fibrosis (CF) diagnosed in premature infants. We describe the clinical course of three patients, from our neonatal intensive care units, who were diagnosed with CF, and discuss the existing literature and treatment considerations.

Keywords

cystic fibrosis; prematurity; lung disease

Introduction

With an incidence of 1 in 3500 live births, cystic fibrosis (CF) is one of the most common life-threatening genetic disorders among Caucasians.[1] It is caused by a mutation in the CF transmembrane conductance regulator (CFTR) protein, a regulatory protein for ion transport. Mutations in CFTR result in multisystem disease of varying severity, affecting the respiratory tract, pancreas, liver, intestines and reproductive tract.

To date, more than 1500 mutations have been described in the CFTR gene (http://www.genet.sickkids.on.ca/cftr/app) but 12 mutations account for 85% of the CF genotypes in North America with the ΔF508 mutation predominating.[2] A new database, CFTR2, is being developed that will assist in linking genotype-phenotype information from patient registries. Diagnosis of CF is either based on symptoms such as recurrent respiratory infections and failure to thrive or through prenatal or newborn screening.[1] Since 2009, all US states conduct CF newborn screening using serum immunoreactive trypsinogen (IRT)

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measured in Guthrie cards. An elevated IRT measurement suggests pancreatic injury consistent with, but not specific for, CF. Depending on the algorithm used, an elevated IRT is followed up either by IRT in a repeat blood sample or by subsequent DNA testing for CFTR genetic mutations on the original blood sample.

We report on three premature infants with CF and their clinical course in our neonatal intensive care unit. We discuss the pathophysiology and therapeutic approaches, which are used in standard CF care but there is little experience of these in premature infants.

Cases

Patient 1

A $24\frac{5}{7}$ week female infant was born via Cesarean section to a 27-year-old G5P1031 woman, secondary to premature onset of labor and fetal distress. Both parents were found to be carriers for CF through pregnancy screening. Prenatal ultrasound showed an echogenic bowel, and amniocentesis confirmed a diagnosis of CF, with homozygosity for the ΔF508 mutation. Birth weight was 0.664 kg (AGA).

Her hospital course was complicated by meconium ileus, bowel perforation and feeding intolerance. She was treated for coagulase-negative *Staphylococcus* and Methicillin-resistant *Staphylococcus aureus* tracheitis/pneumonia. Therapies trialed included a 7-day course of IV dexamethasone, inhaled dornase alfa (recombinant human DNAse) and high-frequency jet ventilation. The patient was ventilator dependent, and died at 40 days of life. Cause of death: ventilator-induced lung injury, chronic lung disease and CF. Autopsy was declined.

Patient 2

A $23\frac{3}{7}$ week female infant was born vaginally to G1P1 29-year-old woman, secondary to preterm labor. Birth weight was 0.510 kg (AGA).

The infant's clinical course was complicated by respiratory distress syndrome, chronic lung disease and ventilator dependence. She had meconium ileus with spontaneous perforation of the small intestine. There were numerous episodes of sepsis; cultures from blood and tracheal aspirate, included *Enterobacter*, *Klebsiella*, *Enterococcus* and Methicillin-resistant *S. aureus*, as well as tracheitis/pneumonia with *Stenotrophomonas maltophilia*. She had presumptive total parenteral nutrition-related cholestatic hyperbilirubinemia and had difficulty tolerating feeds. On the basis of her complicated clinical course, CF genotype was sent that showed two CF mutations (ΔF508/G542X). She was transfered to our hospital for further care and sub-specialty evaluation. Therapies trialed here included dexamethasone (6 days), inhaled dornase alfa, inhaled hypertonic saline and numerous conventional mechanical ventilator modalities. Care was withdrawn after 250 days of life. Cause of death: ventilator-induced lung injury, chronic lung disease, sequelae of CF and multiple pulmonary infections. Autopsy was declined.

Patient 3

A $32\frac{4}{7}$ week twin A male infant of dichorionic/diamniotic pregnancy was born to a G4P1122 35-year-old woman, secondary to preterm labor and premature rupture of membranes. Prenatal ultrasound showed echogenic bowel. Birth weight was 1.993 kg (AGA).

His clinical course was complicated by *in utero* jejunal atresia, volvulus and meconium ileus, and 20% of necrotic small bowel was excised. Genotyping confirmed CF with two ΔF508 mutations. He was intermittently ventilator dependent, secondary to multiple surgical procedures and multiple episodes of sepsis, pneumonia and RSV bronchiolitis. Therapies included inhaled dornase alfa, inhaled hypertonic saline and numerous antibiotic courses. He was discharged home, after prolonged hospitalization, on room air, but has frequent hospitalizations for bronchopneumonia and severe lung disease.

Discussion

We present three patients born prematurely between $23\frac{3}{7}$ weeks and 32 weeks gestation with a diagnosis of CF. All patients suffered from respiratory complications secondary to prematurity, chronic lung disease, pneumonia complicated by ventilator induced lung injury and sepsis. Two patients died from severe lung disease. Each patient had meconium ileus, requiring surgical intervention, which made it difficult to establish enteral nutrition, even after surgical correction. Prolonged use of parenteral nutrition resulted in severe cholestasis in two of the three infants. Pancreatic insufficiency was strongly suspected in all three patients; however, difficulty tolerating enteral feeds precluded the use of pancreatic enzymes. In milder cases of suspected CF, pancreatic enzymes should be used cautiously until pancreatic insufficiency is confirmed by determination of fecal elastase.

There are few reports on prematurity and CF. Sharples and Macek[3,4] report on three premature infants delivered between 24 and 28 weeks of gestation. Each infants' course was complicated by meconium ileus, infections and death from severe respiratory failure at 12, 36 and 80 days of life, respectively. Cystic fibrosis was diagnosed either prenatally secondary to an ultrasound showing echogenic bowel, or postnatally, based on clinical suspicion, prompting a sweat test and serum immunoreactive trypsin test. Festini *et al*.[5] examined all children born with CF in Tuscany ($n = 70$), and compared them with the entire population of non-CF-affected children in a retrospective cohort study conducted over 11 years. They reported a nearly threefold higher risk of being preterm for babies with CF compared with the non-CF population ($P = 0.001$), although no information was provided about their neonatal course.

The combination of prematurity and CF lung disease affects the lung in two major ways. Although chronic lung disease following prematurity mostly affects alveolar function and maturation, early changes in CF lung disease occur in the small-conducting airways, secondary to mucus plugging, inflammation and infection. Conceivably, airway clearance is worsened in very small premature infants and superimposed bronchomalacia, either primary or secondary to ventilator trauma, further complicates the picture. Given the complications of infection and inflammation, targeted antibiotic therapy is often indicated. Despite our lack of studies in this population, mucolytics (inhaled dornase alfa and inhaled hypertonic saline)

should be considered. Inhaled dornase alfa is routinely used to decrease hyperviscous secretions caused by DNA released from neutrophils in CF airways. There are limited data available about its use in premature infants in CF and non-CF patients. Reiter and El Hasseen[6,7] reported on dornase alfa use in premature infants without CF and found that dornase decreased oxygen requirements, decreased mechanical ventilation needs and helped in reestablishing airway patency in premature neonates, with critical pulmonary collapse, secondary to mucous plugging.

Deposition studies reported that the pattern depended on severity of disease in older patients, but that concentration of dornase in children from ages 3 months to 10 years did not depend on patient's age or weight.[8,9] There are no data regarding the dose in the preterm population. The standard dose in the pediatric population is 2.5 ml = 2.5 mg inhaled. The doses used by El Hassan and Reiter[10] included 1 mg m^2, 1.25, 2.5 ml b.i.d., 2.5 mg q.d. We used 2.5 mg b.i.d. in our patients. We cannot assure the dose of dornase was delivered to the lungs nor the distribution in the lungs, however, there did not appear to be evidence of adverse effects, including pulmonary interstitial emphysema. Lastly, one should consider targeted ventilator strategies that minimize trauma and enhance mucus clearance for example, jet ventilation or volumetric diffusive ventilation. In severe cases, the use of corticosteroids could be considered as anti-inflammatory therapy.

Meconium ileus is a frequent complication in premature infants with CF. In term infants with CF, about 10–20% have meconium ileus. Whether premature infants have a higher incidence of meconium ileus is unclear, given the small number of patients studied, nonetheless it remains prudent to consider testing premature infants with meconium ileus for CF, particularly if unusual or worse than expected respiratory symptoms complicate their clinical course. Newborns with CF and meconium ileus tend to have low initial IRT values, resulting in a false-negative screen.[11] Sweat-testing, which is the 'gold standard' for diagnosis of CF is used to confirm or reject infants identified by newborn screening. However, it cannot be reliably performed in infants <36 weeks gestation or <2000 g.[12] Our patients' diagnoses were all confirmed via CF genotyping from serum. Other possible methods for diagnosis include fecal pancreatic elastase if the infant is fed enterally[13] and buccal mucosa DNA[14,15] for CF gene mutation analysis. However, genotype-based diagnosis may miss 10–15% of CF patients depending on genetic background and number of CFTR mutations analyzed.

Despite newborn screening in many countries, there is little information on frequency and outcome of premature infants with CF. The median age of diagnosis is 6 months according to data from the US CF-registry. The new version of the US CF registry, launched in 2010, now includes gestational age and other details on birth history. The French database contains information on birth weight, and they have identified several surviving premature infants with CF (L Lemonnier on behalf of Vaincre la Mucoviscidose, personal communication). With CF databases, available in many countries, inclusion of gestational age will contribute significantly to our understanding of outcomes and the optimal management of premature infants with CF.

In summary, on the basis of cases in the literature, infants less than 28 weeks gestation, with a diagnosis of CF, appear to have not survived the first 3 months of life. Also, when the degree of lung disease in a very preterm infant appears to be more severe than expected, a workup for CF should be conducted.

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