CASE REPORT

Successful survival of an extreme premature infant with cystic fibrosis

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SUMMARY

Extreme premature infants with cystic fibrosis typically do not survive the neonatal phase. This case report describes the youngest survivor of a premature infant with cystic fibrosis and highlights the importance of advanced neonatal care with cystic fibrosis therapy.

BACKGROUND

Outcomes for preterm infants (gestational age <37 weeks) have improved over recent decades with significantly reduced morbidity and mortality. Despite this, extreme preterm infants (<28 weeks) remain at risk of significant pulmonary complications, including early-onset respiratory distress syndrome and long-term neonatal chronic lung disease with resultant loss of functional lung tissue. Cystic fibrosis is the most common life-shortening autosomal-recessive genetically inherited disease of Caucasians, affecting 1 in 2500–3500 live births. It is caused by defects in the cystic fibrosis transmembrane conductance regulator, a chloride channel expressed on the surface of airway epithelial cells as well as in other exocrine organs. Failure to secrete adequate chloride across the airway epithelium results in airway surface dehydration and, consequently, impaired mucociliary clearance. Despite recent therapeutic advances, respiratory failure remains the leading cause of death in cystic fibrosis.

This case highlights that extreme premature infants with cystic fibrosis can survive beyond the neonatal phase. This is primarily due to adjuvant cystic fibrosis therapy along with advances in neonatal care.

CASE PRESENTATION

Dichorionic diamniotic twins were born at 24 weeks of gestation following preterm labour. At birth, twin 1 weighed 510 g and twin 2 weighed 660 g. Both children were immediately intubated and given surfactant.

Twin 2 suffered a complicated course with severe respiratory failure associated with unilateral pulmonary interstitial emphysema, bilateral grade 4 intraventricular haemorrhages and pneumoperitoneum that was conservatively managed. At day 12 newborn screening revealed elevated immunoreactive trypsinogen for both twins and genetic testing confirmed the diagnosis of cystic fibrosis with homozygosity for $\Delta F508$. The parents were counselled towards withdrawal of care but chose to pursue active treatment. Both twins were immediately started on flucloxacillin prophylaxis and then endotracheal nebulised dornase 2.5 mg/day (at day

20) but Twin 2 developed progressive pulmonary collapse/consolidation over several days from 5 weeks of age. Endotracheal aspirates cultured *Enterobacter cloacae*. She was started on broad-spectrum intravenous antibiotic therapy but her clinical status deteriorated further, requiring maximum ventilator support. In light of the progressive respiratory failure and neonatal complications, life-sustaining therapy was withdrawn after extensive discussion with both parents and Twin 2 died.

Twin 1 also had a difficult course over the first months of life. She required 60 days of ventilator support, eventually being extubated to nasal continuous positive airway pressure (CPAP) with concomitant use of dexamethasone and endotracheal dornase. Four months after birth, she was weaned off positive pressure support and started nasal high-flow oxygen before eventually being weaned to 0.5 L/min of infranasal oxygen. Prophylactic antibiotic therapy (flucloxacillin), endotracheal dornase 2.5 mg/day and regular chest physiotherapy were started after cystic fibrosis was diagnosed. In addition, regular nebulised hypertonic saline—initially using 1.5% daily and then increasing to 1.5% two times per day and eventually 3% two times per day—was added to improve airway clearance. Following initiation of dornase, prophylactic flucloxacillin and regular chest physiotherapy, her FiO₂ was able to be weaned from 75 to 26% over the period of a week and she was extubated shortly afterwards. Her neonatal course was complicated with common morbidities of extreme prematurity, including surgical ligation of a patent ductus arteriosus at 3 weeks of age and laser retinal ablation for vision threatening retinopathy at 4 months of age. Her early cranial ultrasound scans were normal whereas a later scan showed bilateral ventriculomegaly. At term, Twin 1 weighed 2210 g (<3rd centile), her length was 42.4 cm (<3rd centile) and head circumference was 31 cm (<3rd centile). She received a total dexamethasone exposure of 14 mg before being weaned. Milk feeding was supplemented with additional caloric and vitamin supplementation with pancreatic enzyme replacement. She was fed via nasogastric tube for 12 months and a feeding gastrostomy was inserted for long-term nutritional management. She was also on diuretic therapy for 4 months with no evidence of nephrocalcinosis on renal ultrasound or urinary electrolytes.

During her prolonged admission, she developed a positive culture for *Pseudomonas aeruginosa* on endotracheal aspirate. This infection was treated

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with 2 weeks of intravenous antibiotics followed by inhaled tobramycin and low-dose oral ciprofloxacin. Eradication was confirmed on subsequent cough sputum specimens and bronchoscopic lavage samples. She was discharged home at her first birthday.

INVESTIGATIONS

Cystic fibrosis genotyping confirms homozygosity for $\Delta F508$.

TREATMENT

1. Supportive ventilation strategies such as invasive ventilation, CPAP and nasal high flow oxygen.
2. Cystic fibrosis therapy, including dornase, hypertonic saline, appropriate antibiotics therapy for lower respiratory tract infections

OUTCOME AND FOLLOW-UP

The surviving twin is now 4 years of age and was weaned off infranasal home oxygen prior to her second birthday. She demonstrates mild developmental delay and is receiving appropriate home-based allied health supports. Her growth percentiles are tracking at along the 3rd percentile for height and weight. High-resolution CT chest at 3 years of age did not demonstrate any bronchiectasis. She has had five inpatient admissions for cystic fibrosis exacerbations which required intravenous antibiotic therapy, including a further successful eradication of *P. aeruginosa*. Spirometry has not been attempted due to the child's current age and developmental delay. Twin 1 has not required further inpatient admission for management of complications of prematurity.

DISCUSSION

In this case study we report the youngest survivor of cystic fibrosis in the literature. The previously reported outcomes of premature infants with cystic fibrosis of <28 weeks gestation have been universally poor—there have been no long-term survivors. Reported outcomes for the handful of premature infants over 32 weeks' gestation with cystic fibrosis, while better, were still complicated with significant morbidity and mortality. The most common cause of death in these cases was secondary to respiratory failure.¹

The previous youngest reported survivors were born at 31/40 weeks² and 32/40 weeks.³ Consequently, there is very little evidence in the literature to guide the management of these infants. While standard cystic fibrosis therapies have been shown to improve long-term outcomes in cystic fibrosis patients, they are not without potential risk in premature, very low birth weight infants. Benefits of initiating therapy need to be weighed against the possibility of potential adverse effects. Some case reports have suggested that the use of mucolytic agents, such as hypertonic saline and dornase alfa, may be beneficial and improve outcomes.⁴ The safety of dornase is not well established in premature infants and the risk of pulmonary haemorrhage is a rare adverse effect. Similarly, hypertonic saline has been reported in case series to be safe and well tolerated with no adverse outcomes.^{2,3} There have also been reports of pancreatic enzyme supplementation improving outcomes in preterm infants with cystic fibrosis.⁴ Even chest physiotherapy has been postulated to increase the risk of brain damage in this population, although systematic review suggests that there is no increased risk of intracranial lesions.⁵ However, given the

respiratory support twin 1 initially required, it was felt that the potential benefits outweighed the risks.

In this case, it is important to consider the complications of prematurity apart from cystic fibrosis. Reassuringly diuretic therapy and subsequent aminoglycoside use for cystic fibrosis respiratory infections have not affected her renal function. Malabsorption and poor weight gain associated with prematurity were compounded by cystic fibrosis in this case and the patient required long-term nasogastric feeds and, eventually, a feeding gastrostomy. A general paediatrician has been involved in the long-term management of this child to assist in the monitoring of development and growth.

Establishing a diagnosis early is important because delay could lead to missed therapeutic opportunities and to worsening of an already poor prognosis.⁴ This case highlights that with recent advances in neonatal care along with appropriate cystic fibrosis therapies such as mucolytics, long-term survival can be achieved in infants with extreme prematurity and cystic fibrosis. In this particular case, it is likely that the instigation of cystic fibrosis treatment has led to improved neonatal outcomes as there was a rapid weaning of respiratory support following its initiation. Families should be appropriately counselled about the likelihood of a poor prognosis but options for active care should be offered as well.

Learning points

- ▶ Early diagnosis of cystic fibrosis through screening and genotyping to enable prompt management care.
- ▶ Long-term survival of extreme premature infants with cystic fibrosis can be achieved.
- ▶ Despite the lack of published evidence, adjuvant cystic fibrosis therapies should be carefully considered and implemented in a premature infant, acknowledging the potential risks of treatment.

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REFERENCES

- 1 Lau C, Ambalavanan N, Chakraborty H, *et al*. Extremely low birth weight and infant mortality rates in the United States. *Pediatrics* 2013;131:855–60.
- 2 Sharples PM, Colditz PB, Wilkinson AR. Lethal respiratory failure in preterm infants due to cystic fibrosis. The first case reports. *Acta Paediatrica Scandinavica* 1989;78:641–3.
- 3 Allen JL, Stavis R, Kaplan GS, *et al*. Diagnosis of cystic fibrosis in a premature infant via neonatal screening. *Arch Pediatr Adolesc Med* 1994;148:995–6.
- 4 Lu KD, Engmann C, Moya F, *et al*. Cystic fibrosis in premature infants. *J Perinatol* 2011;31:504–6.
- 5 Hough JL, Flenady V, Johnston L, *et al*. Chest physiotherapy for reducing respiratory morbidity in infants requiring ventilatory support. *Cochrane Database Syst Rev* 2008 (3):CD006445.

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