Case Report

Cystic fibrosis and trisomy 21, two co-existing genetic syndromes in a newborn: a case report and a review of the literature

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Abstract

A child presenting with the combination of two genetic syndromes, cystic fibrosis and trisomy 21, is rare. Here, we present a case report of a neonate with cystic fibrosis and trisomy 21 and the clinical implications during her course of life. We then review the literature in order to create awareness of co-existing syndromes, to optimize individual patient care, and to help clinicians guide parents in their counselling process.

Introduction

Reports of children with the combination of cystic fibrosis (CF) and trisomy 21 are scarce. To our knowledge, only 8 cases with these co-existing conditions have been previously reported (1-6).

In reviewing the first presenting symptoms of these conditions, we find that meconium ileus (MI) is often the first manifestation of CF. It occurs in 20% of CF patients. MI is most commonly associated with genetic mutations such as class I-III CF transmembrane conductance regulator (CFTR) mutations. Specifically, MI is associated with F508del, G542X, W1282X, R553X, and G551D (7).

Congenital heart disease (CHD) is regarded to be the most important early clinical phenomenon in children with trisomy 21, due to its significant impact on morbidity and mortality. Atrioventricular septal defect (AVSD) is the most common CHD phenotype in these children, followed by ventricular septal defects (VSDs), tetralogy of Fallot (TOF), and atrial septal defects (ASDs) (8).

Pulmonary disease in children with trisomy 21 alone, include recurrent and more severe respiratory tract infections, congenital airway deformations, pulmonary vascular disease, cystic lung disease and sleep apnea. Congenital heart disease, gastrointestinal disease, or need for surgery increases the risk of morbidity and mortality from respiratory illness in these children (9).

Case report

A female infant was born at 33 weeks gestational age. Her mother was a previously healthy 36-year-old Caucasian mother, gravida 4, para 3. The pregnancy concerned a spontaneous triplet gestation, consisting of 2 boys and a girl. The antenatal ultrasound suspected an enlarged colon in the female infant and no deformations in the boys. Antenatal obstetric advice implied no direct perinatal interventions regarding the enlarged colon. Antenatal ultrasound did not detect cardiac abnormalities. Family history for CF was negative. During the pregnancy, there was no noninvasive prenatal genetic test (NIPT) performed.

The children were born in a primary neonatal center at gestational age of 33 weeks by a Cesarean section, this in view of combined risk factors of triplet gestation and preterm labor. The children were well at the time of birth and they did not need immediate life support. The two boys weighed 1.900 kg and 1.890 kg respectively; the girl weighed 1.490 kg, noticeably much lower than her brothers. After birth, the brothers did not present major problems.

On day one of life, the girl presented symptoms of abdominal distention and failed to pass stools. An abdominal X-ray suggested an intestinal obstruction (figure 1). She was referred to our neonatal intensive care for further diagnostics and treatment. An additional X-ray of the colon with contrast enema showed a generalized microcolon (figure 2). Two days after birth the baby had surgery with clearance of the meconium plug. During surgery, an intestinal prenatal volvulus was noticed. The intestines were put in non-rotation and the surgeon constructed an end-to-end anastomosis of ileum and colon.

After surgery the girl showed signs of shock, needing cardiovascular support with intravenous dopamine. On physical examination we detected no heart murmur. Additional echocardiography showed a large ASD, a patent ductus arteriosus (PDA) and a large peri-membranous ventricular septum defect. The baby needed respiratory and cardiac support until day three and day five of life respectively.

Figure 1. Abdominal distention, lower intestinal obstruction

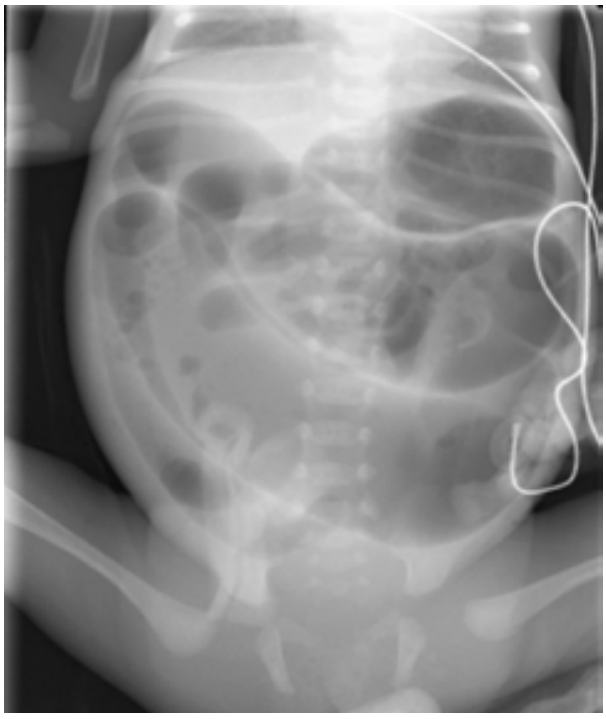
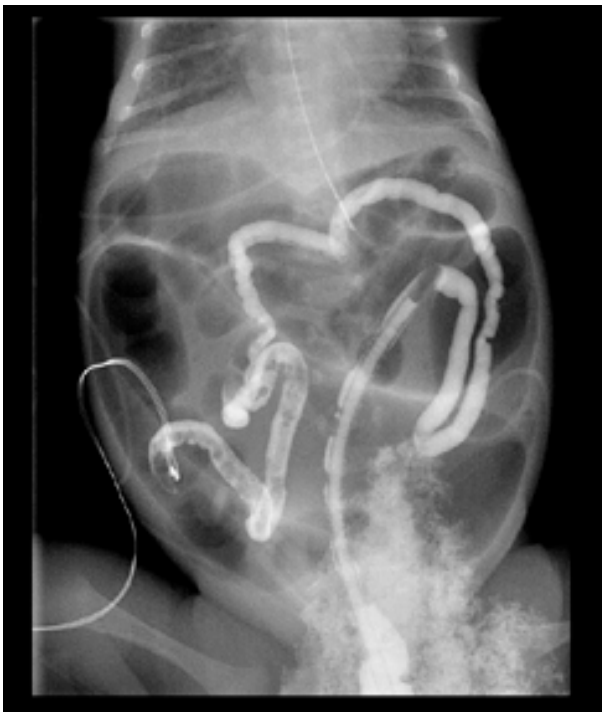


Figure 2. X-ray of the colon with contrast enema: generalized microcolon, meconium plug



In this presentation of a meconium ileus with microcolon, we suspected an underlying condition of CF. Additionally, the baby had minor phenotypic criteria of trisomy 21. She had an epicanthal fold and a palmar crease, though slanting eyes and a broad flat face were not striking in this infant in the premature setting. Also, there was no obvious sandal gap. We did not perform a sweat test because of the gestational age and weight of the infant. Instead, we ordered dual genetic testing for both karyotype and mutations in CF. A homozygous F508del mutation was confirmed at day seven after birth. Trisomy 21 was confirmed at day eight after birth by karyotype.

We initiated minimal enteral feeding at day four and added enteral feeding at day nine.

Still, she failed to pass stools. Enteral feeding failed as re-obstruction of the intestines occurred at day sixteen of life. Initial conservative treatment consisted of ceasing oral feeding, placement of a nasogastric tube and starting IV fluids. She developed fever, and we initiated empiric antibiotic treatment (vancomycin and piperacillin-tazobactam). She had a maximal C-reactive protein level of 222 mg/L (0-5 mg/L). The following days, there was no clinical improvement and as a result, she got surgical discontinuation of ileum and colon.

After initiating enteral feeding, the infant started to experience respiratory distress and progressively needed respiratory support (continuous positive airway pressure (cPAP)). Work-up with a chest X-ray showed a pneumonia, she developed drug-induced thrombocytopenia and antibiotics were converted at day twenty-three of life to IV meropenem. She was then referred to a CF center. They performed a bronchoscopy which showed severe tracheomalacia. Treatment consisted of permanent cPAP. An additional abdominal abscess complicated her illness, which was surgically drained.

Seeing cardiorespiratory decompensation worsened with signs of pulmonary edema at the age of two months, surgical repair of congenital heart disease was planned at a cardiac surgery center. They performed surgical ligation of the PDA and pulmonary artery (PA) banding. Multi-organ dysfunction syndrome and Staphylococcus aureus catheter sepsis complicated her recovery at the intensive care unit. Pulmonary edema persisted and they performed a redo pulmonary artery banding ten days later.

At that point, the girl was three months old. She recovered after her prolonged stay in the intensive care. She then continued her treatment in the center.

In the next few months, she had multiple respiratory exacerbations, all treated with empiric antibiotics. She had respiratory physiotherapy and therapy with nebulized hypertonic saline. Additionally, she had intestinal transit repair. During the following six months, she got intensive respiratory revalidation in a specialized revalidation center.

Follow-up echocardiography at the age of eight months showed that PA banding became too tight. At the age of ten months, the cardiac surgery center performed surgical closure of the VSD and PA debanding. Interaction of postoperative total atrial-ventricular block, persistent pulmonary hypertension, pulmonary edema and chronic lung disease, resulted in insufficient ventilation. After the total atrial-ventricular block recuperated, insufficient ventilation persisted in the next two weeks. Due to the complexity of this case, no clinical improvement after two weeks and the ominous prognosis of her condition, supportive management and end-of-life care were continued after a discussion with the parents. She deceased at 11 months of age. A timeline of her course of life is included in addendum 1.

Addendum 1.

Birth	• 33 weeks post menstrual age. • Birth weight: 1.490kg. • No respiratory support
Day 1-2	• Meconium ileus - generalised microcolon • Surgical clearance of meconium plug • End to end anastomosis • Shock -cardiorespiratory support
D3-5	• Congenital heart disease (ASD/PDA/VSD) • Minimal enteral feeding
D7-8	• confirmation: homozygous F508del mutation resulting in cystic fibrosis • confirmation of trisomy 21 karyotype
D9-18	• Failure of enteral feeding • IV piperacillin-tazobactam-vancomycin • Construction of stoma and enterocutaneous fistula
D23	• Pneumonia - IV meropenem • Bronchoscopy: severe tracheomalacia
2months	• cardiac decompensation; pulmonary edema • PA banding, surgical ligation PDA • Persistent pulmonary edema -redo PA banding
3 months - 10months	• multiple respiratory exacerbations • transit repair • respiratory revalidation
10 months-11 monts	• VSD repair -PA debanding • cardiorespiratory decompensation- pulmonary edema - AV block - pulmonary hypertension • Death

Discussion

Reports of co-existing CF and trisomy 21 are scarce. Incidence in Belgium of CF is 1:3500 live births and of trisomy 21 is 1:1400 live births (10,11). The risk of co-occurrence in Belgium is 1:4.900.000. The birth rate in Belgium is approximately 117.000 newborns per year (data of 2018) (12). This means a similar new case might occur every 41 years.

To our knowledge, no other report of a Belgian child is previously made. The prognosis for these children, with exception of one case report, is poor and they did not survive infancy or childhood (1-6).

Children with trisomy 21 alone have a vulnerable pulmonary vasculature that may manifest clinically as pulmonary hypertension, pulmonary edema or pulmonary hemorrhage. They develop more acute pulmonary edema , an indication of the fragility of pulmonary capillary integrity. Diffuse parenchymal lung disease manifests in these children as chronic radiographic changes associated with persistent findings such as dyspnea, cough, wheezing, crackles, or hypoxia. They have an increased risk of respiratory tract infections and are relatively more likely than children without trisomy 21 to have a severe course and even death from respiratory causes. In the subgroup of patients with trisomy 21 who had surgery, risk of respiratory infection was approximately three times higher than for children with trisomy 21 who did not have surgery. Additional congenital heart disease or gastrointestinal disease was a risk factor for admission for respiratory illness independent of undergoing surgery. Pneumonia was the single most common respiratory disorder, accounting for 43% of admissions to the intensive care unit. The pathophysiology underlying the increased risk for respiratory disease in children with trisomy 21 remains unclear, but a variety of immune defects have been identified (9).

Lung disease in children with CF is responsible for the vast majority of morbidity and mortality. Until recently, the standard of care in CF treatment focused on preventing and treating complications of the disease; now, novel treatment strategies targeting the ion channel abnormality directly are becoming available.

The interaction of the pathophysiology of lung disease in trisomy 21 with the pathophysiology in CF has not been studied, since the literature on this topic consists only of case reports. Still, it is not unlikely that novel treatment strategies in CF might improve the outcome in combined genetic syndromes as well.

Conclusion

Our case is the first case of a neonate with the co-existence of CF and trisomy 21 as a part of a triplet pregnancy, consisting of otherwise two healthy boys. This report highlights the possible co-existence of two genetic diagnoses in a newborn. The severity of co-morbidities in either of these conditions and the interplay between them might predict the possible outcome. Although more prospective and even prenatal research is needed, our case report underlines the impact of the diagnosis in the neonatal course of life. Therefore clinicians should be aware of the possibility of this co-existence of syndromes.

Conflicts of interest

Authors declare no conflict of interest.

Human research statement

Parental oral informed consent is obtained.

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