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Fellow Column: An Unbalanced Translocation Involving Partial Duplication of Chromosome 6 and Partial Deletion of Chromosome 10 in a Premature Infant with Tetralogy of Fallot

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Abstract

Purpose: To report a case of simultaneous chromosome 10 partial deletion and chromosome 6 partial duplication in a preterm infant.

Methods: This is a retrospective case report followed with clinical observation, echocardiogram, and genetic testing.

Results: A neonate with Tetralogy of Fallot, clubbed feet, low set ears, and webbed neck was found to have chromosomal abnormalities that are consistent with unbalanced translocation between chromosomes 6 and 10, resulting in a partial duplication of chromosome 6 and partial deletion of chromosome 10.

Discussion: Chromosome microarray testing in a patient with multiple congenital anomalies can facilitate rapid diagnosis and treatment with the potential to improve the management of complications and subsequent development.

Introduction

Prematurity is commonly associated with respiratory distress syndrome, patent ductus arteriosus, apnea of prematurity, hypoglycemia, and fetal exposure to drugs of abuse. Prematurity is also common in neonates with structural cardiac anomalies, limb abnormalities, and facial dysmorphism. We report a preterm infant treated in the neonatal intensive care unit with chromosome 6 and 10 abnormalities.

Methods

A retrospective chart review was performed on a patient who presented to the Emanate Health Queen of the Valley Neonatology Intensive Care Unit (West Covina, CA) following the preterm delivery of a twin gestation. Subsequent growth, developmental, cardiac, and musculoskeletal anomalies were monitored in the NICU.

Case Report

Baby M is a 36 week and 1-day gestation infant born to a 20-year-old Hispanic G2P1 woman who is blood type O positive. The mother's first pregnancy led to premature delivery and rapid demise of an infant with multiple congenital abnormalities. In the second pregnancy, dichorionic diamniotic fraternal twins with intrauterine growth restriction (smaller twin B; Baby M) were diagnosed with club feet and congenital heart disease on prenatal ultrasound. There was persistent absent end-diastolic flow in twin B. Due to suspected fetal anomaly and fetal distress; a cesarean section was performed.

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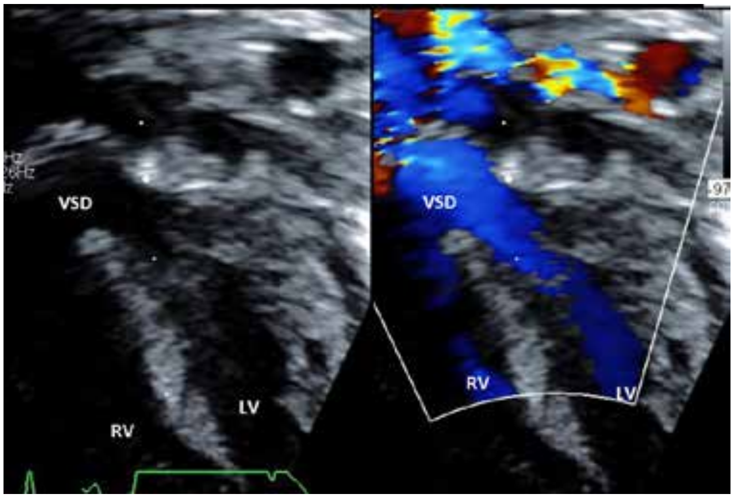
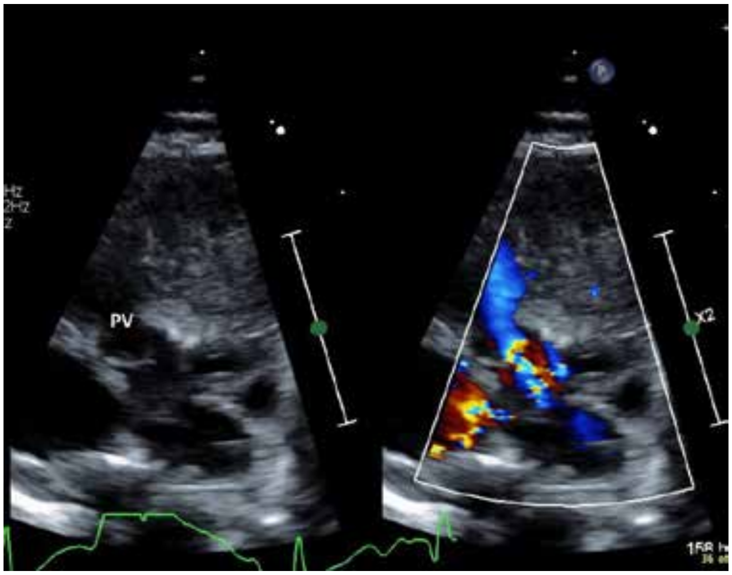
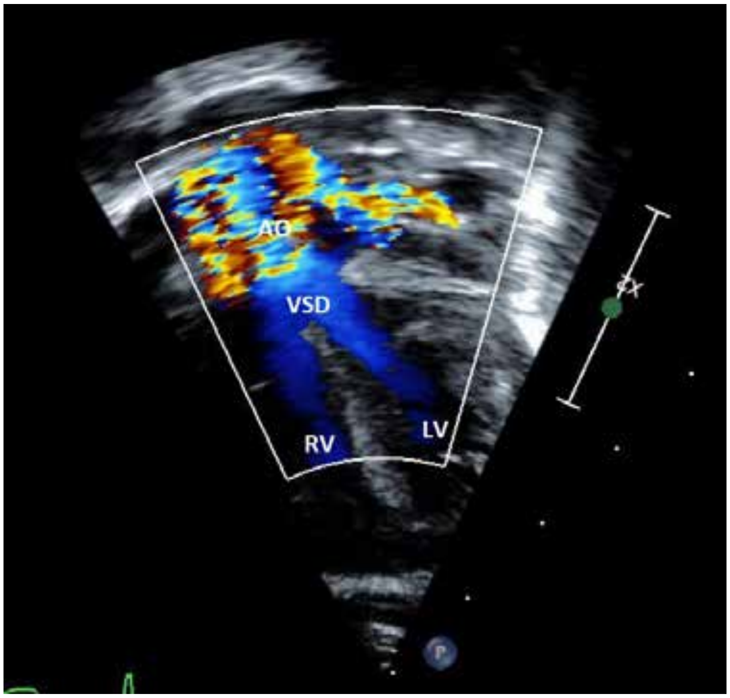
The mother underwent general anesthesia, and amniotic fluid was clear. The presentation of this patient was breech. The baby had poor respiratory effort and required supplemental O_2 with positive pressure ventilation. APGAR scores were 5 and 9 and 1 min and 5 min, respectively. Following delivery, the mother and the patient's twin were stable and were discharged without any significant complications.

Clubfoot [internet]. Wikipedia [cited Sep 17 2020]. Available from: https://commons.wikimedia.org/wiki/File:Pied_bot,_varus_%C3%A9quin_(bilateral).jpg.

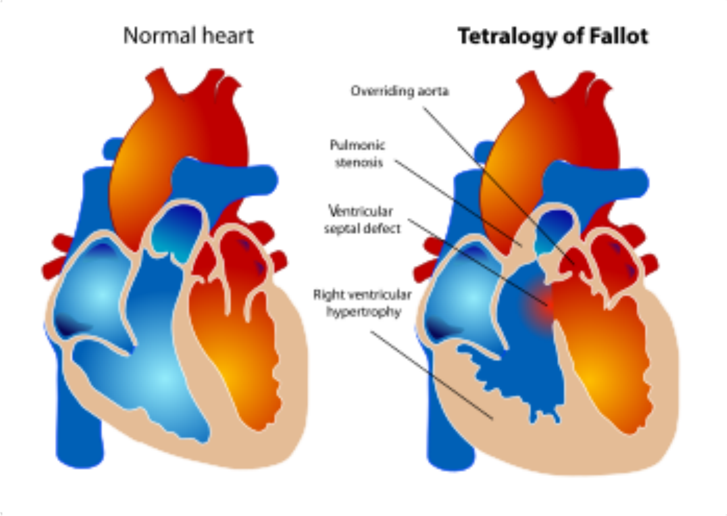
This 36 weeks gestation female was small for gestational age for all growth parameters: birth weight was 1255 g (<3%tile), head circumference was 26.5 cm (<3%tile), the length was 38cm (<3%tile). The temperature was 36.1, the heart rate was 152, the respiratory rate was 79, and the blood pressure was 57/25. The chest had mild to moderate retractions in the substernal and intercostal areas consistent with prematurity. Breath sounds were clear and equal bilaterally. There was a 4/6 systolic murmur throughout the precordium. Other significant features were micrognathia, webbed neck, contracted fingers, club feet, low set ears, and epicanthal folds. The abdomen was soft and flat with normal external genitalia. The baby had bilateral club feet. Her hips were stable. She responded to tactile stimulation with diminished tone and decreased spontaneous activity. The skin was pink and adequately perfused. The infant was managed on non-invasive ventilation. She was placed on NPO on admission and started on IV D10 at 100ml/kg/day. The baby had initial hypoglycemia that resolved with IV therapy. The baby advanced to full cycled feeds of PE 24hp. There were no known maternal risk factors for infection. The baby had hyperbilirubinemia of prematurity and received phototherapy. The infant had no unusual movements or seizure-like activity.







Echocardiogram images courtesy of Dr. John Ho



Tetralogy of Fallot [internet]. Wikipedia [cited Sep 17 2020]. Available from: https://commons.wikimedia.org/wiki/File:Tetralogy_of_Fallot.svg

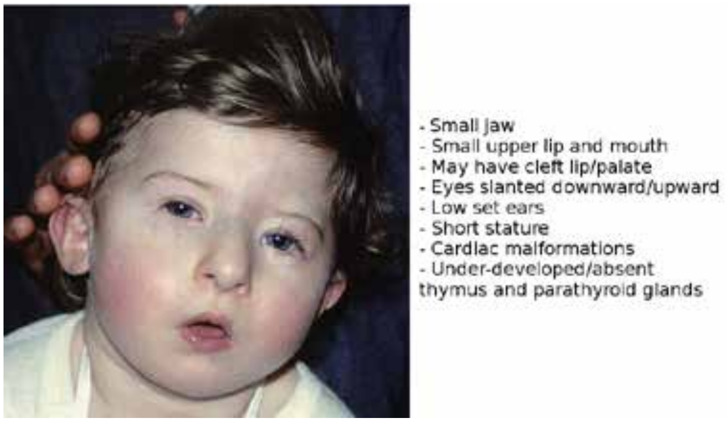
Echocardiograms on day of life 3 and 19 revealed Tetralogy of Fallot with large outlet VSD and overriding aortic root, PFO, ASD, PDA, aortic stenosis, bicuspid aortic valve, pulmonic stenosis, and thick and doming pulmonic valve. The infant was started on Furosemide at 13 days. She underwent routine chromosome analysis with a “reflex” chromosome microarray. Abdominal ultrasound and retinal exams were within normal limits. Serology negative for HIV, Rubella, and Hepatitis B. When the baby reached 2 kg, she was transferred to a tertiary center for further evaluation and heart surgery.

Initial chromosome analysis (LabCorp) was abnormal with extra material of unknown origin on the short arm of chromosome 10: 46,XX,add(10)(p15.1). SNP chromosome microarray (LabCorp) microarray analysis identified a terminal duplication of chromosome 6q and a terminal deletion of chromosome 10p. Microarray testing found a 28.5 MB duplication on chromosome 6 6q24.1 → q27 and a 3.8 MB deletion on chromosome 10 at 10p15.3→p15.2, consistent with an unbalanced translocation. Chromosome 6 duplication involved genes *PITRMI* and *ZMYNDII*. The chromosome 10 deletion involved *NMBR* g. The presence of a terminal gain and terminal loss of different chromosomes in the same analysis suggests that the proband may have inherited a single unbalanced derivative chromosome 10 from a parent with the balanced translocation between the two chromosomes. The lab recommended specific FISH analyses for the parents to investigate possible familial genetic rearrangements.

Discussion

Parents who have balanced chromosome translocations may be asymptomatic, while their offspring with unbalanced translocations may have complex congenital anomalies. Unbalanced translocations can also lead to infertility, miscarriage, or life-threatening congenital anomalies. Baby M’s mother had a previous stillbirth, which raises concerns that this translocation is familial, and the mother may carry a balanced version of the t(6;10) translocation. There have been reported cases of chromosome 6;10 translocations, resulting in miscarriage, suggesting that the stillbirth before baby M may have been a result of an inherited unbalanced translocation. [1]

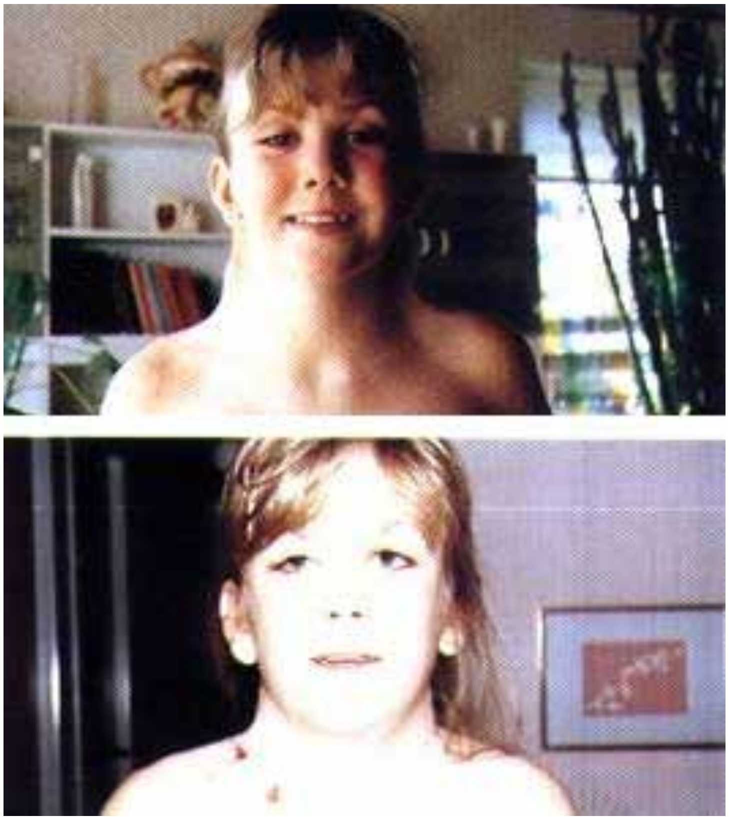
The twin gestation with Baby M was dichorionic and diamniotic, suggesting that these were fraternal twins, conceived from different gametes. While baby M had a birth weight of 1255g, twin A was born at almost twice her birth weight and was discharged without any significant anomalies. Because the mother may have had a balanced translocation, further testing was recommended in her. If a familial translocation can be confirmed in one of the parents, further testing is warranted for the asymptomatic twin A who is also at risk to carry a balanced version of the familial translocation. Understanding the results of the microarray analysis can help explain the features of this patient and can potentially help predict future development.



Digeorge Syndrome [internet]. Wikipedia [cited Sep 17 2020]. Available from: https://commons.wikimedia.org/wiki/File:DiGeorge_syndrome1.jpg

Deletions in chromosome 10p yield a range of variable symptoms and findings. Associated features include severe intellectual disability, growth delays, short neck, and congenital heart defects. [2] Several cases have also been reported in patients with features of DiGeorge syndrome. DiGeorge syndrome, which is a common feature of the 22q11.2 deletion syndrome, presents with the triad of conotruncal heart defects, hypocalcemia, and absent thymus. While the genetic origins of this patient's condition are distinct from DiGeorge syndrome, cardiac anomalies, epicanthal folds, short necks, and widely spaced nipples are similar and point to possible common pathophysiology. Absent thymus, absent parathyroid glands, and possible hypocalcemia in other patients with similar genetic abnormalities have been described.

Specifically, this patient's 10p15.3→p15.2 deletion includes the genes *PITRM1* and *ZMYND11*. *PITRM1* codes for an ATP-dependent metalloprotease that degrades post-cleavage mitochondrial transit peptides. [4] The protein binds zinc and can also degrade amyloid beta A4 protein, which suggests a possible link to Alzheimer's disease. *ZMYND11* codes for a zinc finger protein that localizes to the nucleus and functions as a transcriptional repressor. [5] Specifically, it is known to bind the adenovirus E1A protein. Deletion of these genes, causing haploinsufficiency for the gene products, could contribute to manifestations related to Alzheimer's and Adenovirus infection in this patient.



Turner Syndrome [internet]. Wikipedia [cited Sep 17 2020]. Available from: https://commons.wikimedia.org/wiki/File:Neck_of_girl_with_Turner_Syndrome_(before_and_after).jpg

Duplications in chromosome 6q are extremely rare and can present with growth retardation, mental retardation, webbed neck, musculoskeletal abnormalities, clubbed feet and hands, wide-spaced nipples, scoliosis, and internal organ manifestations. [3] This patient has features that are consistent with the phenotype associated with chromosome 6q duplication, including the webbed neck, clubbed feet, and wide nipples. The specific 6q24.1→ q27 duplication involves *NMBR*. This gene encodes for a 7-transmembrane G protein-coupled receptor that binds neuromedin B, a growth factor, and mitogen for gastrointestinal epithelial tissue and normal or neoplastic lungs. [6] This receptor plays a role in smooth muscle contraction, neuronal responses, and cell growth regulation. This gene may also be associated with schizophrenia. Taken together, this patient's chromosome 6 abnormalities may increase the risk for neurodevelopmental problems such as intellectual disability and schizophrenia.

Conclusion

In this report, we describe a patient with an unbalanced translocation that is likely to be familial. The chromosome 6q 624.1 → q27 duplication and chromosome 10 10p15.3→p15.2 deletion increase risk for a variety of anomalies that include abnormalities of the thymus, parathyroid glands, and calcium levels. Monitoring for scoliosis and schizophrenia could be warranted later in life. Furthermore, in neonates presenting with signs of Down syndrome or DiGeorge syndrome, evaluation for an unbalanced translocation with chromosome microarray may be warranted. Taken together, this has potential implications for the course of treatment and preparing the patient and parents for complications that may arise in the future.

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