A Case of Mosaicism in a Prenatally Diagnosed Down Syndrome Neonate

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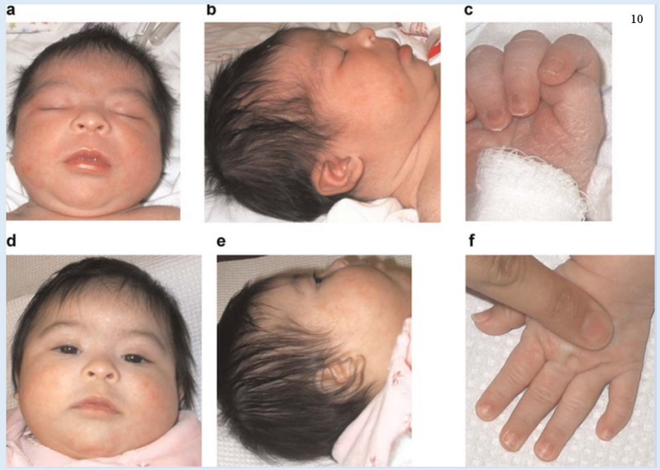
Introduction

- Down syndrome (DS), also known as trisomy 21, is the most common chromosomal condition diagnosed in the US[1]
- Clinical Manifestations of DS include low-set ears, flat facial profile, epicanthal folds, excess skin at the nape of the neck, simian crease, sandal gap deformity, hypotonia, decrease DTR, atrioventricular septal defects, duodenal atresia, intellectual disability, acute lymphocytic leukemia (ALL), and atlanto-axial instability[2]
- Mosaicism is defined as the presence of two or more distinct cell lines from a single zygote (one cell line being trisomic, the other being euploid)[3]
- Mosaic DS occurs in 2-4% of all DS cases[4]
- People with Mosaic Down syndrome (MDS) often have less severe clinical features of DS compared to other DS karyotypes[2, 3, 5, 6]
- Lymphocyte chromosomal analysis is a better indicator for predicting phenotypes of a mesodermal origin and buccal chromosomal samples are better predictors for phenotypes of ectodermal origin[3]

Table 4. Numerical relationship between percentage of trisomic cells[a] and number of phenotypes in mosaic DS cases[a]. [2]

Trisomic cells (%)	Number of phenotypes present
90	13
90	15
80	9
80	12
70	11
70	15
60	8
60	10
50	6
50	12
50	11
25	4
25	10
25	9
18	3
10	5
10	5



Newborns with MDS may have subtle phenotypes of DS including horizontal palpebral fissures, epicanthal folds, broad nasal bridge, micrognathia, excess skin at nape of neck, and clinodactyly

Hospital Course

DOL 0: Admission to NICU
- CPAP support
- UVC placed and TPN started
- Cord blood sent for chromosome analysis

DOL 1
- OG tube placed and trophic feeds started
- CPAP weaned and caffeine started

DOL2
- Holosystolic murmur heard at LSB
- Phototherapy started for increased bilirubin

DOL 6
- UVC removed/TPN discontinued
- Fortified breast milk

DOL 9
- CPAP weaned to room air

DOL 63: Discharged at 40 wks corrected gestational age
- 1L NC
- Breast milk fortified to 24 calories
- Cardiology follow up for grade III/VI murmur
- Follow up with genetics clinic

Case Description

Maternal History
- 40 yo G2P0111 IVF pregnancy initially dichorionic-diamniotic twins with loss of twin at 7 weeks gestation

Delivery History
- Fetus with severe fetal growth restriction (birth weight 1220 g) with reverse end diastolic flow
- Fetal amniocentesis confirmed DS
- Fetal echocardiogram significant for 2 small ventricular septal defects (VSD)
- Delivery via primary cesarean at 31 wks gestation for non-reassuring fetal heart rate and reverse end diastolic blood flow
- Required CPAP support
- Antenatal steroids with rescue dose and Mg sulfate given prior to delivery
- 1 min APGAR – 7
- 5 min APGAR - 8

Newborn Physical Exam
- General: Weak cry, Down syndrome features
- HEENT: Bilateral upward and outward slanting palpebral fissures, well positioned ears, relatively large tongue, palate intact
- Lungs: Course crackles bilaterally via auscultation, respirations slightly labored on CPAP
- Cardiac: No murmurs
- Vascular: Strong and equal femoral pulses
- Extremities: Faint simian crease bilaterally. Wide gap between big toe and second toe bilaterally
- MSK/Neuro: Symmetric bilateral hypotonia, hyporeflexia and strength. Positive mild root and suck

Diagnostic Results
- Chest X-ray day of life (DOL) 1: mild respiratory distress syndrome (RDS)
- Echocardiogram DOL 19: Innocent flow murmur. Structurally normal heart with patent foramen ovale which is normal for age. No VSD. No patent ductus arteriorsus. No coarctation of the aorta.
- Chromosomal analysis: 47, XX, +21 [15], 46, XX [5]
- Three independent copies of chromosome 21 were observed in 15 of 20 metaphases. The remaining 5 metaphases were apparently normal. The phenotype associated with trisomy 21 mosaicism can range from normal to classic Down syndrome.

Discussion

- Mosaicism is more common in other chromosomal abnormalities, but is rare in Down syndrome[7]
- The severity of clinical features of MDS cannot be accurately predicted for the patient due to polygenetic variability, however, there is a statistically significant correlation between the percentage of trisomic cells and the severity of DS features[2]
- Source of the chromosomal sample for the patient was cord blood which may be a better predictor for the phenotypes of mesodermal derived tissues[3]
- Referral to a genetic specialist is important as MDS patients have a higher mortality rate from leukemia compared to congenital heart disease[8]
- Referral to early intervention is important for discharge as children with MDS tend to have higher IQs and meet developmental milestones sooner than other DS karyotypes[5,6, 9]
- People with Mosaic DS more often achieve a higher education level and have a full-time job than non-mosaic trisomy's[9]

Conclusion

- MDS is a rare form of DS that can vary in severity of phenotypic characteristics, but all people with DS have equal risk of leukemias
- The source of the chromosomal sample may be a better predictor for certain phenotypes of Down syndrome due to their embryologic germ layer derivation and multiple samples should be taken prior to diagnosis
- Early intervention is important for improved outcomes and activities of daily living

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