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Diagnostic dilemma caused by overlapping features of Prader-Willi syndrome and trisomy 18 during infancy

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To the Editor:

The report by Miller et al¹ effectively illustrates the difficulty in early diagnosis of Prader-Willi syndrome (PWS). They describe 6 newborns with hypotonia who were not diagnosed with PWS until an average age of 17 months. We would like to draw attention to 3 additional infants with dysmorphic hypotonia, demonstrating similarities between PWS and other congenital disorders (eg, trisomy 18).

Our first subject was a 20-month-old girl referred because of developmental delay and growth retardation. Prenatal history was significant for a choroid plexus cyst, identified by routine sonography, and decreased fetal movement. She was born at term, weighing 2.8 kg (10th centile), and was 49.5 cm (30th centile) long. She had hypotonia, respiratory distress, and significant feeding difficulties requiring tube feedings. Ear tubes were placed in early infancy because of chronic infections. Strabismus was present by 1 year of age. She sat at 1 year, crawled at 15 months, and spoke a few words at 20 months, at which time her height was 78.8 cm (10th centile), weight 9.27 kg (5th centile), head circumference 46.1 cm (25th centile), and hand length 9 cm (3rd centile). She also had a narrow bifrontal diameter, dolichocephaly with mild ridging of the sagittal and metopic sutures, almond-shaped eyes, a

small mouth with down-turned corners and a thin upper lip, a short nose, narrow appearing hands, a systolic murmur (small ventricular septal defect), and hypotonia (Figure). PWS was considered because of these findings and chromosome testing performed with fluorescent in situ hybridization analysis. Trisomy 18 mosaicism (47,XX,+18 [23 cells]/46,XX [27 cells]) was found with no evidence of a 15q11-q13 deletion. Results of DNA methylation analysis were normal. Trisomy 18 is a classical malformation syndrome with features common to PWS including decreased fetal activity, weak cry and suck, narrow bifrontal diameter, small mouth, cryptorchidism, hypoplasia of the labia majora and skeletal muscle, growth retardation, and developmental delay.

In addition, 2 other infants with PWS who were followed up in our clinics were initially thought to have trisomy 18 during the newborn period. The first was a male newborn with hypotonia, now with typical features of PWS at 15 months of age. He presented at birth with severe hypotonia, a large fontanelle, wide nasal bridge, narrow bifrontal diameter, small mouth, prominent occiput, dorsiflexion of the great toes, low-set ears, bilateral cryptorchidism, and a high arched palate. Trisomy 18 was considered the most likely diagnosis. Although initial chromosome studies showed a normal chromosome number, a 15q11-q13 deletion was detected by high-resolution analysis and confirmed by fluorescent in situ hybridization. The second newborn with hypotonia, now a 4-year-old girl with typical features of PWS, was initially thought to have trisomy 18. Results of routine chromosome studies during the newborn period were normal; however, maternal disomy 15 was identified by molecular genetic analysis, confirming PWS.

Thus, our 3 subjects with features of both PWS and trisomy 18 further illustrate the inherent diagnostic difficulties in newborns with hypotonia and the counseling dilemma raised by families awaiting specific genetic test results. The etiology, prognosis, and management options of these 2 classical cytogenetic syndromes are quite different.

Reference

1. Miller SP, Riley P, Shevell MI. The neonatal presentation of Prader-Willi syndrome revisited. *J Pediatr* 1999; 134:226–8. [PubMed: 9931534]

Figure.
Frontal view of 20-month-old female subject with trisomy 18 mosaicism.