The Genetics Corner: A Genetics Consultation for Agenesis of the Corpus Callosum and Poor Feeding

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Case History:

A genetics consultation was requested for a 4-day old term SGA female with poor feeding, who was prenatally diagnosed at 30 weeks gestation with IUGR and agenesis of the corpus callosum, raising concern for holoprosencephaly. The baby was conceived by intrauterine sperm injection (IUI). She was born by repeat C-section to a 29-year-old G5 P1 SAb3 mother at 39 weeks gestation. BW 2829 grams (12th %ile), HC 32.5 cm (10.6th %ile). Apgar scores were 8 at one and 9 at five minutes. She required occupational therapy to assist with oral feedings, and the NG tube was used for gavage. Brain MRI at one day of age confirmed agenesis of the corpus callosum without other CNS anomalies. Echocardiogram revealed a large PDA and PFO. Chromosome microarray was pending.

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The family history was negative for consanguinity and other affected children. The mother reported that all five of her pregnancies were with the same partner. Their only other living child was conceived with IVF.

The physical exam revealed a small, mildly dysmorphic female with a large nevus flammeus on her forehead. She had several unusual facial features: large, soft anterior and posterior fontanels, down-slanting palpebral fissures, periorbital puffiness, a beaked nose with columella that extended below the alae nasi, mild micrognathia and a small posterior cleft of the soft palate. Her thumbs were broad and deviated. Her great toes were broad but not deviated. Her tone was mildly decreased.

Consultant's Report:

This baby has Rubinstein Taybi syndrome (RTS), a distinctive autosomal dominant disorder with a reported prevalence of 1/125,000 live births, which is likely to be underreported due to incomplete ascertainment. Most patients are sporadic with a negative family history. The cause of infertility in this family is unclear and may be unrelated to the diagnosis of RTS.

The diagnosis of RTS is based primarily on characteristic clinical features although there are no established diagnostic criteria. The diagnosis should be suspected in an infant with broad, angulated or abducted thumbs and great toes, a feature that is present in 96% of infants with RTS. The typical facial features, which are present in 100% of infants with RTS, include down-slanting palpebral fissures and a columella that is lower than the alae nasi. A narrow, high palate is typical but a cleft palate, which was present in this patient, is an uncommon finding in RTS. A vascular nevus on the forehead is a common sign. Growth parameters are near normal at birth, but growth retardation begins within the first months of life. Feeding is often poor due to hypotonia and gastroesophageal reflux. Agenesis or dysplasia of the corpus callosum occurs in many patients with RTS. Other CNS anomalies, Chiari I and Dandy-Walker malformation, hydrocephalus, instability of C1-C2 and tethered cord have been reported. Seizures are present in 25%.

Congenital anomalies have been reported in most organ systems, including the heart (24-38%: ASD, VSD, PDA, Ao coarctation, AS, PS, HLHS), kidneys (52%), GI (40-74%: reflux, constipation, megacolon), and eyes (cataract, coloboma, glaucoma, strabismus), justifying a detailed evaluation in the affected newborn. Hearing loss (conductive and sensorineural) and obstructive sleep apnea can be diagnosed and treated in infancy. Moderate intellectual disability, microcephaly and short stature are typically evident in childhood. Various childhood cancers (e.g., neuroblastoma, medulloblastoma, rhabdomyosarcoma, leukemia) have been reported.

Figure 1: Note the abducted and angulated thumbs, downslanting palpebral fissures and low hanging columella in this infant with Rubinstein Taybi Syndrome. The glabellar nevus flammeus is a helpful though nonspecific sign.

Genetic tests are useful for the diagnosis of RTS, but they may not be informative. The diagnosis can be confirmed with genetic testing in 50-70% of patients with RTS. Pathogenic variants or copy number changes involving two genes, CREBBP at 16p13.3 and EP300 at 22q13, occur in 60% and 10% of cases respectively. These two genes interact closely and both act in chromatin

remodeling. Chromosome analysis and microarray may identify structural rearrangements or copy number variants at 16p13.3 or 22q13.

Figure 2: Broad, radially deviated thumb

Interestingly, preeclampsia is common among the mothers of infants with RTS due to a variant in EP300, occurring in ~25%.

Practical applications:

1. Suspect RTS when there are broad or angulated thumbs or great toes with suggestive dysmorphic facial features, hypotonia, poor feeding or other anomalies.
2. Evaluate infants suspected of RTS for congenital anomalies in other organ systems with an echocardiogram, abdominal US, ophthalmologic exam, audiology evaluation, head ultrasound or brain MRI.
3. Expect poor feeding and, when present, evaluate for GE reflux.
4. Use syndrome-specific growth charts for infants with RTS.

Figure 3: Broad great toes

5. Consider gene testing for CREBBP and EP300 (order sequencing and deletion/duplication analysis) when RTS is suspected clinically.

References:

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The authors have no relevant disclosures.

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How to Care for a Baby with NAS

Use the Right Words

I was exposed to substances in utero. I am not an addict. And my mother may or may not have a Substance Use Disorder (SUD).

Treat Us as a Dyad

Mothers and babies need each other. Help my mom and me bond. Whenever possible, provide my care alongside her and teach her how to meet my needs.

Support Rooming-In

Babies like me do best in a calm, quiet, dimly-lit room where we can be close to our caregivers.

Promote Kangaroo Care

Skin-to-skin care helps me stabilize and self-regulate. It helps relieve the autonomic symptoms associated with withdrawal and promotes bonding.

Try Non-Pharmacological Care

Help me self-soothe. Swaddle me snugly in a flexed position that reminds me of the womb. Offer me a pacifier to suck on. Protect my sleep by "clustering" my care.

Support Breastfeeding

Breast milk is important to my gastrointestinal heath and breast feeding is recommended when moms are HIV-negative and receiving medically-supervised care. Help my mother reach her pumping and breastfeeding goals.

Treat My Symptoms

If I am experiencing withdrawal symptoms that make it hard for me to eat, sleep, and be soothed, create a care plan to help me wean comfortably.

Learn more about
Neonatal Abstinence Syndrome
at www.nationalperinatal.org

National Perinatal Association