Genetics Corner: Multisuture Craniosynostosis Secondary to Intrauterine Constraint During Gestation in a Bicornuate Uterus

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A 10 year 8-month-old. Female status post sagittal and metopic craniosynostosis was seen for an initial genetic evaluation in the Craniofacial Team Clinic. Her Spanish-speaking mother provided the history through an interpreter.

She was the product of her 27-year old mother's first pregnancy. The gestation was complicated by a maternal bicornuate uterus and vaginal spotting at ~2 months' gestation when the pregnancy was detected. An ultrasound exam was suspicious for a subchorionic hemorrhage. Fetal movements were reduced, and the fetal position was always "transverse." The mother denied teratogenic exposures, illnesses, and diabetes. She gained about 15 lbs in the pregnancy.

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The infant was delivered at 38 weeks by scheduled C-section for breech presentation. Birth weight was 6 lb 3 oz. She was admitted to the NICU for two weeks primarily for hypoglycemia and respiratory distress. CT scan confirmed metopic and sagittal craniosynostosis at ten days of age. She was referred to the craniofacial clinic when she was 2 ½ months of age. At six months of age, cranial remodeling surgery was aborted for excessive bleeding and blood loss. Brain MRI at ten months showed mild scaphocephaly and turricephaly and was otherwise normal, without evidence of a vascular anomaly. Surgery was successfully performed at 14 months of age. Early milestones were delayed. She walked at two years of age and said her first words at 2 1/2 to 3 years of age. However, at age 10, she is doing well in the 5th grade, attending GATE (gifted and talented) classes.

The family history was non-contributory. Parental consanguinity was denied. She has one healthy 4-year old brother. Parents, who are both 37 years old, are of Hispanic ancestry from Mexico. There is no other reported family history of birth defects, developmental delay, intellectual disability, early infant deaths, or multiple miscarriages.

She was an alert, cooperative, well-spoken and nondysmorphic

school-aged child with normal growth parameters on the exam. There was mild bitemporal narrowing. Her fingers were tapered, but the remainder of the exam was normal.

Assessment and counseling:

This child has multisuture craniosynostoses involving the metopic and sagittal sutures without other congenital anomalies or dysmorphic features. It is most likely that her craniosynostosis is secondary to fetal head constraint and abnormal mechanical forces related to gestation in a bicornuate uterus (Figure 1). Uterine malformations are relatively common, affecting up to 7% of the female population and 18% of women with recurrent pregnancy loss. Approximately 1-2% of women have a significant uterine abnormality (Moh *et al.* 2010) that poses a 30% general risk for fetal deformation. In their case-control study from 75 participating hospitals in Spain, Martinez-Frías *et al.* analyzed the outcome of 38 pregnancies (32 liveborn) in women with a bicornuate uterus noting a four-fold increase in congenital anomalies compared to women without a uterine anomaly. However, their data did not reach statistical significance for any particular anomaly (except nasal hypoplasia), possibly because of the limited sample size. The mothers with a bicornuate uterus also had significantly more uterine bleeding during pregnancy (54.1% vs. 14.1%), increasing the risk for some types of vascularly-mediated anomalies (disruptions), such as limb defects.

"Intrauterine constraint causes fetal deformation by applying abnormal mechanical forces to the developing fetus, altering the shape of the trapped body parts. A fetal constraint has been implicated in the etiology of plagiocephaly, torticollis, micrognathia, limb contractures, pulmonary hypoplasia, congenital hip dislocation, talipes equinovarus, and craniosynostosis."

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Intrauterine constraint causes fetal deformation by applying abnormal mechanical forces to the developing fetus, altering the shape of the trapped body parts. A fetal constraint has been implicated in the etiology of plagiocephaly, torticollis, micrognathia, limb contractures, pulmonary hypoplasia, congenital hip dislocation, talipes equinovarus, and craniosynostosis.

Over 40 years ago, Graham and Smith (the same Smith who authored "Smith's Recognizable Patterns of Human Malformation") and various colleagues published a series of reports illustrating the relationship between fetal head constraint and metopic, coronal, and sagittal craniosynostosis. They published what may have been the first report of metopic craniosynostosis in the child of a woman with a bicornuate uterus. In the same report, they described metopic craniosynostosis in one of monozygotic triplets reared in a small mother in which the affected fetal head had been wedged between the hips of the two unaffected siblings. In 1980, Higginbottom *et al.* reported five infants with craniosynostosis who had evidence of intrauterine constraint, including breech presentation, primigravidity, uterine malformations, amniotic bands, and defects in fetal neuromuscular development.

In 2010, Sanchez-Lara *et al.* reported fetal constraint as a risk factor for some types of craniosynostosis. Specifically: plurality and nulliparity were associated with a twofold increased risk for metopic craniosynostosis. Macrosomia had almost twice the risk of developing coronal craniosynostosis.

In our patient, genetic testing was not recommended. Based on her mother's history of bicornuate uterus, the lack of a family history of craniosynostosis, the absence of other congenital anomalies or dysmorphic features, and her normal or even superior developmental outcome, the chance of a genetic etiology for her craniosynostosis would be too low to justify the cost of the testing. Note that the patient's brother was unaffected, perhaps because he had the advantage of gestating in the somewhat larger parous bicornuate uterus.

Practical applications:

1. Infants born to women with uterine anomalies, such as a bicornuate uterus, may have a higher rate of congenital anomalies. Examine these infants carefully for deformations and vascularly-mediated disruptions.
2. Suspect intrauterine constraint in the etiology of craniosynostosis in the context of a breech or transverse lie, bicornuate uterus or other scenarios that restrict fetal movement, especially in a primigravida mother.
3. Fetal head constraint can cause craniosynostosis of any suture and even multiple sutures as in this child.

Figure 1. Types of bicornuate uterus malformation. Attribution: Wikimedia User: EternamenteAprendiz (CC BY-SA 4.0 <https://creativecommons.org/licenses/by-sa/4.0/deed.en>)

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Figure 1

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Which Infants are More Vulnerable to Respiratory Syncytial Virus?

RSV is a respiratory virus with cold-like symptoms that causes 90,000 hospitalizations and 4,500 deaths per year in children 5 and younger. It's 10 times more deadly than the flu. For premature babies with fragile immune systems and underdeveloped lungs, RSV proves especially dangerous.

But risk factors associated with RSV don't touch all infants equally.*

*Source: Respirator Syncytial Virus and African Americans

Caucasian Babies	Risk Factor	African American Babies
11.6%	Prematurity	18.3%
58.1%	Breastfeeding	50.2%
7.3%	Low Birth Weight	11.8%
60.1%	Siblings	71.6%
1%	Crowded Living Conditions	3%

AFRICAN AMERICAN BABIES bear the brunt of RSV. Yet the American Academy of Pediatrics' restrictive new guidelines limit their access to RSV preventative treatment, increasing these babies' risk.

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