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The Genetics Corner: Perisylvian Polymicrogyria and Seizures in One of Monochorionic Diamniotic Twins Following Twin-Twin-Transfusion Syndrome and *in utero* Laser Ablation Therapy

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A Case History:

I was asked to evaluate a 6-month old female, Twin B, one of a 31-week gestation monochorionic diamniotic twin pair, with recent onset of myoclonic jerks. Seizures had begun the previous week with staring episodes, during which her eyes rolled back, and she lost tone. She became more irritable with reduced appetite. Hypsarrythmia was present on video EEG. Brain MRI showed bilateral perisylvian cortical dysplasia and periventricular leukomalacia. Chromosome microarray analysis was normal.

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Prenatal History:

The mother denied prenatal exposure to drugs, alcohol, or tobacco. A maternal-fetal medicine specialist had followed her because she was carrying monozygotic monochorionic diamniotic (MCDA) twins. At 19 weeks and two days gestation, she was referred for fetoscopic laser surgery because of twin-twin transfusion syndrome (TTTS) and selective IUGR in Twin B, the donor twin. The placental cord insertion site was marginal for Twin B and eccentric for Twin A. The intertwin weight discordance at that time was 22%. Twin B had intermittent absent end-diastolic flow. In reviewing the options for therapy, the mother was given a risk of 4% for cerebral palsy or other neurodevelopmental impairment following selective laser photocoagulation of communicating vessels. The mother elected to proceed with laser surgery, and all aberrant vessels were coagulated at 20 weeks' gestation, approximately three months prior to delivery. Following the procedure, fetal US monitoring every two weeks documented normal interval growth and normal amniotic fluid volumes in both twins. By one month after the procedure, Twin B's estimated weight was greater than Twin A's. No fetal anomalies were appreciated in either twin.

Birth History:

The twins were delivered at 31 weeks 0 days gestation despite tocolytic therapy. Spontaneous rupture of membranes occurred 3 hours prior to delivery. The patient, Twin B, was born by vertex vaginal delivery through brown amniotic fluid to a 28-year old G6 P3 Ab3 SAb1 mother. Birth weight was 1690 grams (73rd %ile), BL 42.5 cm (85th %ile), HC 27.9 cm (50th %ile). Apgar scores were 91 and 95.

Newborn Course:

The baby was initially NPO. She started enteral feeds on DOL#2 and advanced to full feeds over a week. She received total parenteral nutrition for seven days. She started nippling at 19 days of age and tolerated all feeds by mouth with adequate weight gain by discharge. She was on high flow nasal cannula for five days, gradually weaning from 2L to room air. She did not require central lines. Hg and Hct were normal at birth. She received 48 hours of empiric antibiotics (IV Ampicillin and Gentamicin) with no clinical sign of infection except a purulent eye discharge (E.coli) on DOL#2, treated with five days of Tobrex. She required phototherapy for indirect hyperbilirubinemia. Her highest bilirubin levels were 8.2/0.3 on DOL#7.

Importantly, there were no focal deficits on the neurological exam in the newborn period. Initial head US on DOL#7 was read as negative; however, the repeat head US at six weeks of age showed distorted brain parenchyma on the right that was also noted, in retrospect, on the initial head US. A brain MRI was suggested, but it was not done as she was discharged two days later at 47 days of life.

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Imaging Studies:

In Figure 1, the head US image from 6 weeks of age shows the distortion of the right lateral ventricle, with a sulcus coursing through it, which was interpreted as secondary to a sulcal variant or possible developmental anomaly. An MRI of the brain was recommended.

In Figure 2, images from the brain MRI with and without contrast at six months of age show congenital bilateral perisylvian syndrome with polymicrogyria/cortical dysplasia of the bilateral frontoparietal lobes and mild periventricular leukomalacia, compatible with prematurity. The radiologist's interpretation noted "cortical thickening and loss of normal sulcation in the bilateral frontoparietal lobes, with superiorly elongated sylvian fissures. The right sylvian fissure extends deep into the high right frontoparietal region, with overlying cortical thickening and focal indentation of the lateral margin of the right lateral ventricle. There is periventricular white matter volume loss, adjacent to both lateral ventricle bodies, with mildly dysmorphic lateral ventricular margins, and thinning of the corpus callosum. There is mild prominence of the lateral third, and fourth ventricles, and mildly prominent subarachnoid spaces over both cerebral hemispheres."

Family History:

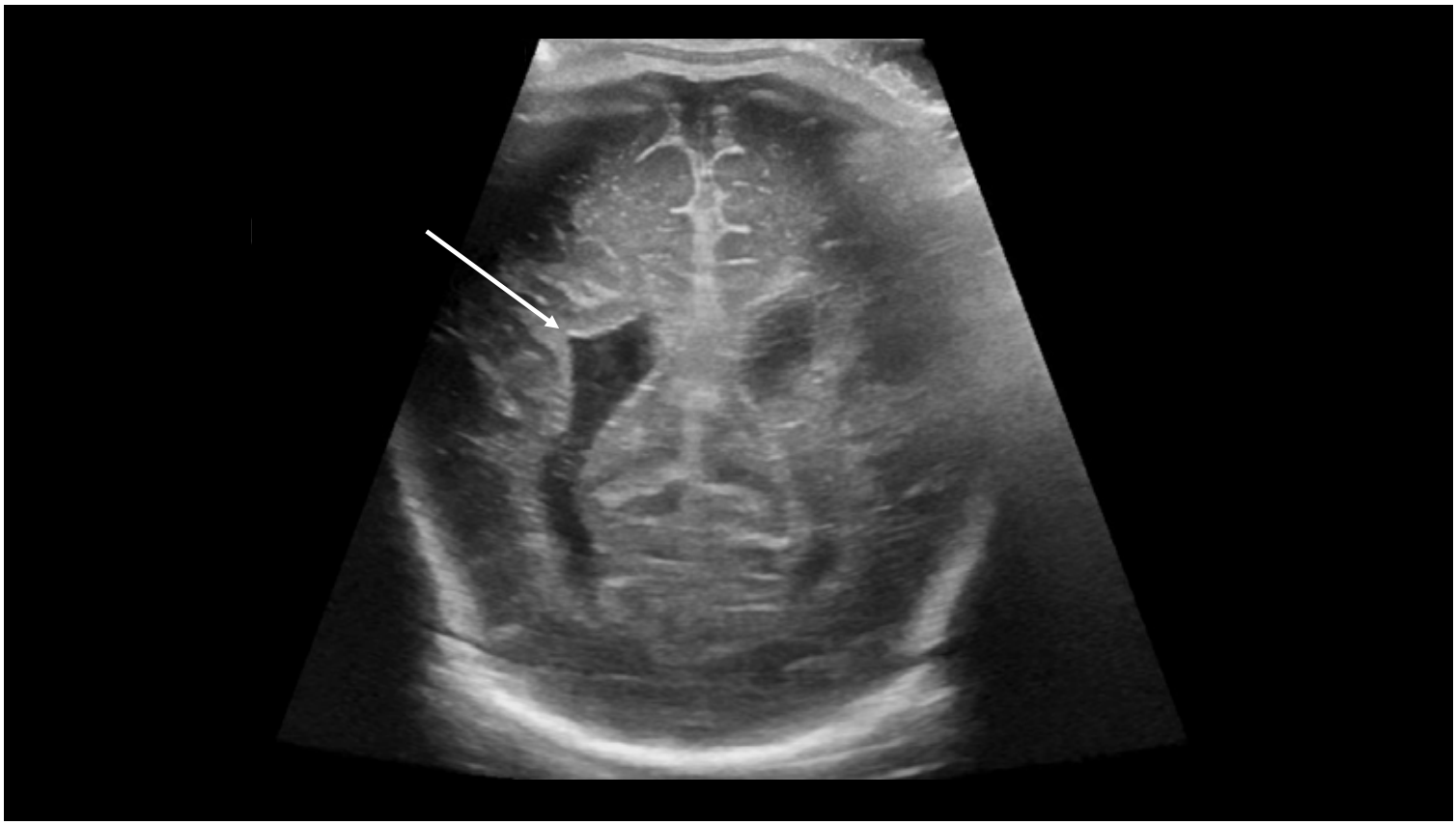

Figure 1: Coronal ultrasound at six weeks of age demonstrates irregularity of the right ventricular margin (white arrow).

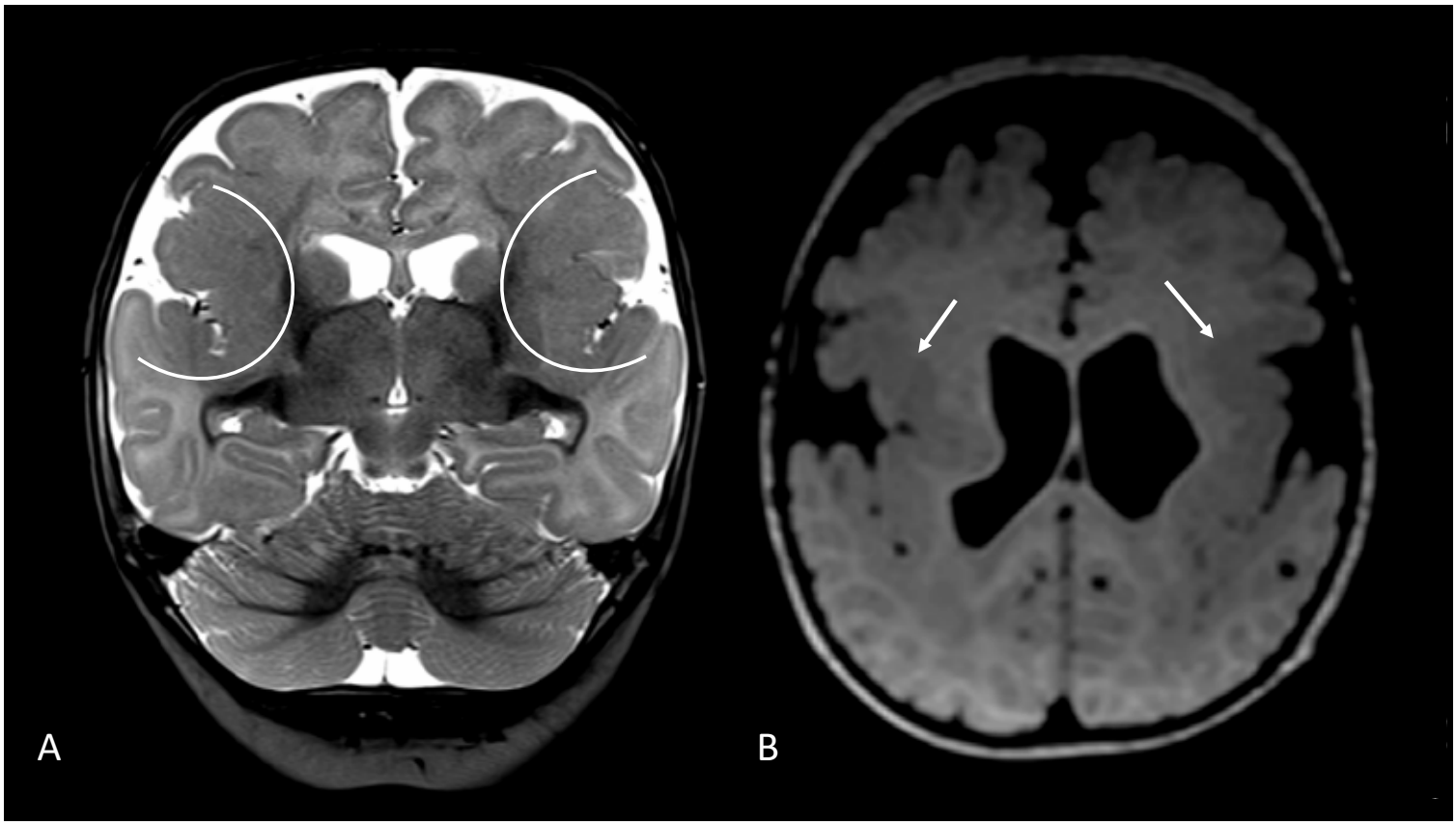

Figure 2: Coronal T2 weighted image at six months of age (A) demonstrates bilateral perisylvian cortical dysplasia (white curves). Axial FLAIR image (B) demonstrates perisylvian cortical dysplasia (white arrows). Also noted is periventricular white matter volume loss with scalloping of the ventricular margins, consistent with periventricular leukomalacia.

This patient's identical twin sister is in good health and is on target developmentally. Parents are 29 (mother) and 20 (father) years old. There is no other family history of birth defects, developmental delay, intellectual disability, early infant deaths, or multiple miscarriages. Parents are of Hispanic ancestry from Mexico. Parents denied consanguinity.

Physical Exam:

The exam was pertinent for microcephaly. The head circumference was 41 cm, <1st %ile, Z-score -2.79. For comparison, her co-twin's HC was 45 cm. Her features were not dysmorphic. She had adducted thumbs and clenched hands and toes. The neuro exam was abnormal with poor visual attention, generalized hypertonia, and hyperreflexia.

Assessment and Counseling:

Twin-twin transfusion syndrome (TTTS) occurs in 10-15% of all monochorionic multiple pregnancies with high perinatal mortality and morbidity (D'Antonio, et al. 2020). In the severe forms, diagnosed at 16-26 weeks gestation, fetoscopic laser selective coagulation of placental anastomoses is an established first-line treatment. This therapy offers the hope of survival to twins at grave risk of intrauterine death, but it is not without significant risks. Intact survival after laser ablation for TTTS varies from 47 to 68%. Many case series have established that neurodevelopmental outcome is adversely affected. In the series reported by Gray (2011), 12% of survivors of TTTS laser ablation surgery had a neurodevelopmental impairment, 4% had cerebral palsy, and 8% had an intellectual disability. Other authors have reported higher rates of disability with cerebral palsy in 6-13% and developmental disability in 13-18%.

In general, an overall survival rate of 50-70% can be expected after laser therapy, while the risk of abnormal neurodevelopmental outcome ranges between 4 and 18% (van Klink et al. 2016). Both donor and recipient twins are at increased risk for brain damage following laser ablation. Laser ablation for TTTS caused structural brain damage that was evident on fetal MRI at 30-32 weeks in 2% of 113 long-term survivors (Stirnemann et al. 2018). These authors found that certain structural CNS anomalies occur more commonly among fetuses with TTTS, especially those with a vascular etiology such as leukomalacia, ischemia, infarct, ventriculomegaly, porencephaly, schizencephaly, and polymicrogyria. Banek (2003) reported hemiparesis, spastic quadriplegia, infantile spasms, infarction of the middle cerebral artery, nystagmus, and cerebral palsy among a group of survivors with more severe neurological sequelae. Schou (2019) reported severe neurodevelopmental impairment in 9/86 children with TTTS who were treated with fetoscopic selective laser coagulation when they were examined at 25 months, compared to 3.1% in a control group of monochorionic twins from uncomplicated pregnancies.

TTTS also poses risks to the fetal brain on its own. Cerebral ventricular dilation, presumed to be due to white matter injury and intraventricular hemorrhage, has been documented on fetal brain imaging for TTTS before laser ablation. Postnatal factors such as low gestational age at birth also contribute to neurodevelopmental impairment. Disability is significantly higher for twins born prior to 32 weeks gestation. In this patient, the head US suggested an asymmetric lesion at one month of age, but a brain MRI was not performed until the infant presented several months later with infantile spasms.

The parents were counseled that their daughter's seizure disorder was due to her brain anomalies, especially the bilateral perisylvian polymicrogyria, that were caused by vascular insufficiency during gestation secondary to TTTS and laser ablation. This explains the discordance between this patient and her unaffected identical twin sister, who does not have seizures or developmental delays. If her neurological and developmental problems were due to a genetic etiology that she shared with her MZ twin sister, we would expect both twins to be concordant for the phenotype. However, discordance is more common and even expected among surviving twins who were treated for twin-twin-transfusion syndrome with laser ablation. Dr. Bill Dobyns, an expert at the University of Washington, has seen 25 such discordant twin pairs with TTTS after laser ablation that have similar structural CNS anomalies, including schizencephalic brain clefts and polymicrogyria without a genetic etiology (personal communication).

In this scenario, when MZ twins are discordant for a CNS anomaly, and when the brain anomalies themselves are asymmetric, a genetic etiology is unlikely, and attention should shift to other causes, especially vascular insufficiency. The recurrence risk for a similarly affected (singleton) offspring born to these parents is low. When confronted with a CNS anomaly, these factors should raise suspicion for a vascular etiology:

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1. One of a set of Monoamniotic-Dichorionic MZ twins with shared vascular anastomoses
2. Twin gestation with a history of TTTS
3. History of in utero laser therapy
4. Premature delivery at 31-weeks gestation
5. Asymmetric brain anomaly

Practical Applications:

1. Consider a vascular etiology whenever MZ twins are discordant for CNS anomalies
2. Understand the limits of head US imaging.
   a. Do not rely on the head US to identify all CNS anomalies, such as polymicrogyria.
   b. Follow up an abnormal head US with brain MRI prior to discharge whenever possible.
3. Consider routine brain MRI on all survivors of TTTS regardless of neuro status or history of laser ablation therapy.
4. Monitor both twins when there is a history of TTTS, with or without laser ablation.
   a. Anticipate an increased risk for adverse neurological and developmental outcomes such as seizures, spasticity,

and developmental delay

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Acknowledgment:

The authors wish to thank Dr. Sheri Handler for her expert assistance in the selection and annotation of the ultrasound and MRI images in figures 1 and 2.

The authors have no relevant disclosures.

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