The Genetics Corner: A Consultation for Multiple Congenital Anomalies

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Case History:

A 1-day-old 33 week gestation male infant was evaluated for multiple congenital anomalies that were diagnosed prenatally on fetal ultrasound. Fetal MRI at 32w5d showed micrognathia with associated glossoptosis, absent right kidney, short right upper extremity suggestive of absent right humerus, bilateral short lower extremities suggestive of absent femora with clubbed feet. Pelvic osseous structures and sacrococcygeal segments were suspicious for caudal regression syndrome.

The infant was delivered by emergency C-section at secondary to a placental abruption and maternal preeclampsia to a 25 year old primigravida mother. The parents had been trying to conceive for 5 years prior to this conception. The pregnancy was complicated by maternal insulin-dependent diabetes mellitus diagnosed in the 9th week of gestation. Insulin therapy was started in the first trimester. Mother was obese at 170 lbs pre-pregnancy weight and gained 20 lbs during her pregnancy. First trimester HgbA1c levels were unavailable for review. Apgar scores were 31 and 85.

Birth weight: 1.5 kg (3 lb 4.9 oz) (10th percentile)
Birth length: 28 cm (0th percentile)
Birth head circumference: 30.5 cm (60th percentile)

In addition to the prenatally diagnosed anomalies, the infant had Pierre-Robin sequence with cleft palate. He also had a bicuspid aortic valve and bilateral inguinal hernia. He required a tracheostomy for severe micrognathia and a gastrostomy tube. Chromosome microarray analysis was normal. He was in the NICU for two months primarily for respiratory issues and growth. He was referred for bilateral abnormalities on the newborn hearing screen and was subsequently diagnosed with mild hearing loss.

The family history was significant for type 2 diabetes in both maternal grandparents.

Genetics Evaluation:

On physical exam, the infant had facial dysmorphism: a round face, square forehead, short nose with prominent nasal tip, bilateral epicanthus, long philtrum, cleft palate, micrognathia and thin lips. He had absent femurs and absent right humerus with multiple vertebral segmentation anomalies with 5 lumbar vertebrae, a questionable fusion of L4-5 and 2 sacral vertebral segments. Both feet were clubbed. Abdominal US revealed a solitary right kidney. Xrays confirmed absence of the right humerus, left humeral-ulnar fusion, and absence of both femora.

This infant has the typical phenotype of femoral facial syndrome, also known as femoral hypoplasia unusual facies syndrome (FFS). This rare, variable and sporadic multiple congenital anomaly syndrome (OMIM 134780) is not associated with any known genetic variant. The initial report (1) described 4 patients with a similar phenotype of femoral hypoplasia and characteristic facial features with micrognathia, cleft palate, short nose with broad nasal tip, long philtrum and thin upper lip. Abnormalities of the genitourinary tract, dysplastic sacrum and vertebral anomalies are also reported. Associated central nervous system anomalies can include hydrocephalus and corpus callosal abnormalities.

Although maternal pregestational diabetes was not noted in the initial report, subsequent reports have documented a strong relationship between maternal diabetes in pregnancy and femoral facial syndrome. In a recent review of FFS, 50.8% of patients with FFS in a Brazilian cohort were infants of diabetic mothers (2).

That report also describes a discordant monozygotic (MZ) twin pair, which is evidence against a Mendelian gene disorder. MZ twins can be discordant due to a number of different mechanisms. There can be unequal allocation of cells as early as the blastomere stage, genetic discrepancies (post-zygotic changes, chromosome mosaicism) and epigenetic mechanisms due to imprinting and X-chromosome inactivation (in females). There is one report of an affected father having an affected daughter, but all other cases have been sporadic.

"Epigenetic mechanisms may underlie the variability in both the range of birth defects as well as the incomplete penetrance of the phenotype in diabetic embryopathy."

Maternal diabetes is a well-known human teratogen that causes several different patterns of congenital anomalies, which are collectively referred to as diabetic embryopathy. Diabetic embryopathy is associated with poor maternal glycemic control in the first trimester of pregnancy (3). The risk for birth defects is increased to about 10% in infants of diabetic mothers (IDMs) whereas the background risk is 3% (4). The risk for malformations is higher in women with pregestational diabetes and is inversely related to the degree of maternal diabetic control, as measured by maternal serum hemoglobin A1c levels (HgbA1c) (5).

Epigenetic mechanisms may underlie the variability in both the range of birth defects as well as the incomplete penetrance of the phenotype in diabetic embryopathy. Epigenetic modifications are heritable changes in gene expression without a change in the underlying nucleotide sequence. This is achieved by a combination of DNA methylation, histone modifications and non-coding RNAs, which contribute to mitotic memory. It is an important mechanism facilitating the differentiation of cells during embryonic development (6, 7).

In animal studies, the cellular mechanisms responsible for diabetic embryopathy include increased cellular apoptosis and protuberance of the temporal pattern of gene expression during embryonic

Figure 1: Characteristic findings of femoral facial syndrome: round face, short nose with bulbous nasal tip, long philtrum, thin upper lip. Short lower extremities (absent femurs), short right upper extremity (absent humerus)

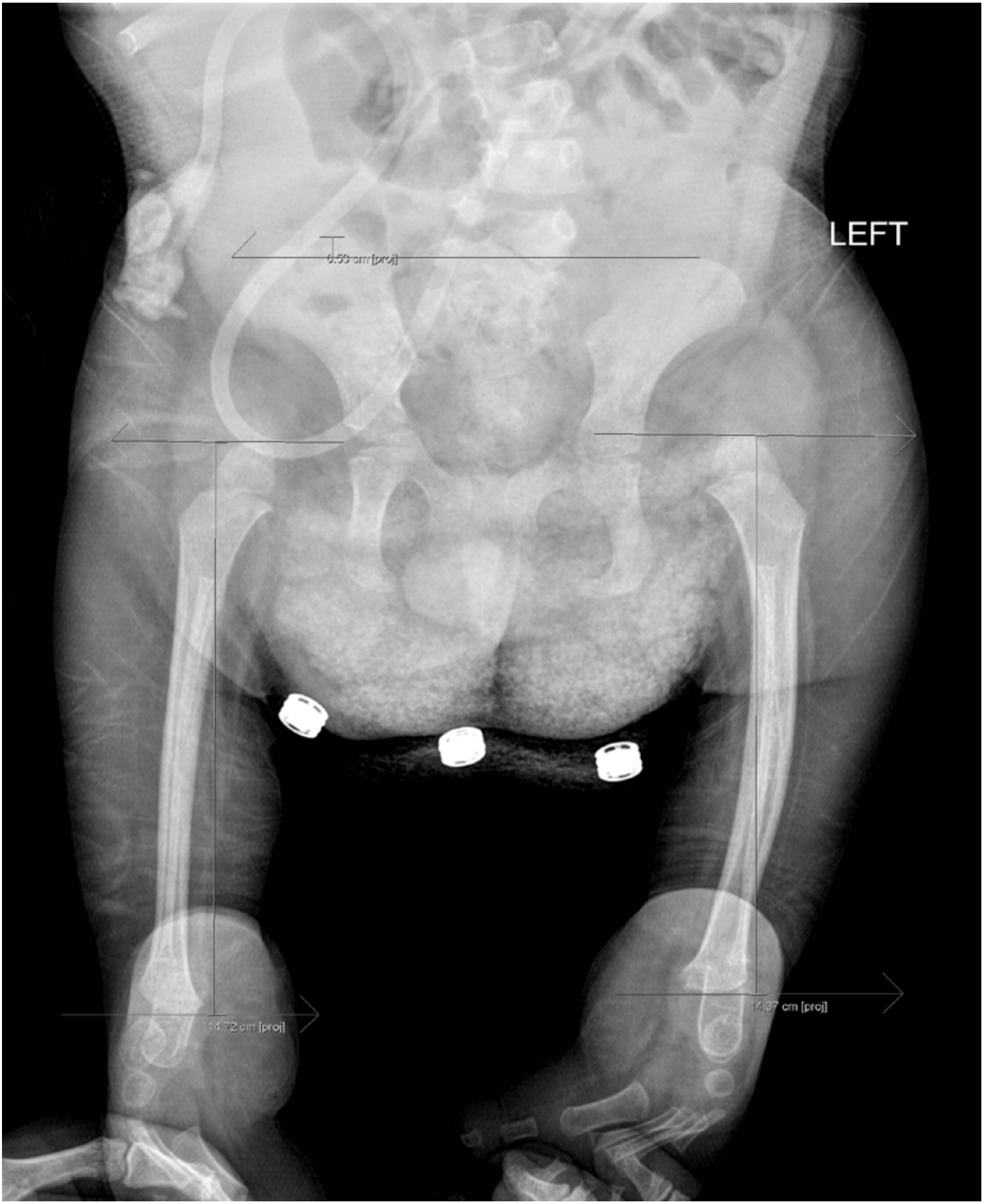

Figure 2: Absent femurs, wide pubic symphysis, shortened/ dysplastic sacrum, bilateral clubbed feet

development. The disturbance may happen only during hyperglycemic peaks in maternal circulation, but these can be sufficient to cause permanent, irreversible changes during critical periods of fetal morphogenesis (8). Administration of supplemental folic acid has been shown to ameliorate diabetic embryopathy in animals.

"Diabetic women should be encouraged to plan all future pregnancies and to be in excellent diabetic control prior to conception, optimally with a HgbA1c level between 5.7- 5.9."

Conclusion and Counseling:

Infants of diabetic mothers are at a higher risk for birth defects. The highest window of susceptibility for fetal malformations is in the first 4 weeks of pregnancy, which is strong recommendation for counseling diabetic women to optimize their diabetic control prior to conception. Blastogenic malformations and first trimester miscarriages are the most common adverse effects of diabetic embryopathy (9). Infertility is more common among gestational diabetics, as was the experience in this young mother (10).

The recurrence risk for diabetic embryopathy in a future pregnancy in a mother with pregestational diabetes, who has had a prior affected pregnancy, is increased over 10%. Diabetic women should be encouraged to plan all future pregnancies and to be in excellent diabetic control prior to conception, optimally with a HgbA1c level between 5.7- 5.9. The greater the level of control, the less the potential risk to the pregnancy and the lower the risk for miscarriage and infertility as well as congenital anomalies. The diabetic mother-to-be should start prenatal vitamins and supplemental folic acid (4mg/day) beginning at least a month prior to any future conception. The latter recommendation also addresses the increased risk for open neural tube defects in infants of diabetic mothers.

Practical applications:

- Femoral facial syndrome is highly associated with maternal diabetes.
  - o It should be suspected when one or both femora are hypoplastic or absent in an IDM.
- There is no known genetic etiology for this disorder.
  - o Epigenetic variants may play a role by creating a permissive environment that fosters the teratogenicity of hyperglycemia.
- Poorly controlled maternal diabetes is one of the strongest human teratogens, tripling or more the chance of birth defects
- Counsel diabetic mothers to achieve good diabetic control prior to conception to reduce the risk for diabetic embryopathy.
  - o Recommend monitoring maternal HgbA1c levels prior to gestation and early in the first trimester.
  - o Counsel diabetic women of child-bearing age on the increased risk for congenital anomalies when diabetes is poorly controlled in early pregnancy.
  - o Encourage diabetic mothers to take folic acid daily starting prior to conception.
  - o Recognize that miscarriage and infertility are associated with gestational diabetes mellitus.

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The authors have no relevant disclosures.

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