The Genetics Corner: DiGeorge Anomaly Associated with Diabetic Embryopathy in an Infant without a Deletion on Chromosome 22q11

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Case History:

A genetics consult was requested for a one-week-old female infant with prenatally diagnosed complete atrioventricular (AV) canal defect. The pregnancy was complicated by maternal pregestational diabetes mellitus, which was poorly controlled in the first trimester, indicated by a maternal hemoglobin A1c level of 11.7.

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The infant was delivered at 37 weeks gestation by emergency C-section for failure to progress after spontaneous rupture of membranes.

Birth weight: 3050 g (6 lb 11.6 oz)
Birth length: 50.5 cm (19.88")

Birth head circumference: 34 cm (13.39")

Apgar scores were:

1 (0 color, 0 reflex, 0 resp, 0 tone, 1 HR) at 1 minute.

8 (1 color, 2 reflex, 2 resp, 1 tone, 2 HR) at 5 minutes

The congenital heart defect was confirmed postnatally with an unbalanced right-dominant atrioventricular canal with moderate AV valve regurgitation and aortic arch hypoplasia with coarctation. In addition, the infant had a solitary kidney and vertebral anomalies.

The infant underwent Norwood operation with aortic arch reconstruction at two weeks of age. Chromosome microarray analysis was normal. A G-tube was placed for poor oral intake and concern for aspiration

Genetics Evaluation:

Because of restrictions due to the coronavirus pandemic, this evaluation was performed remotely by video in the cardiac intensive care unit. The family history was significant for pregestational maternal diabetes mellitus and advanced paternal age (father was 50 at delivery).

The infant was nondysmorphic and did not have the characteristic facial features associated with 22q11.2 deletion syndrome. There was moderate scoliosis with a lower thoracic curve, concavity to the left, corresponding to the vertebral anomalies evident on chest X-ray: T8 butterfly vertebra and right T11 hemivertebra. MRI L-spine showed a tethered cord (terminating at L3-4) with an associated fatty filum that merged with a sacral lipomeningocele. An Ophthalmology evaluation was normal.

She had hypocalcemia, secondary to hypoparathyroidism, and thymic aplasia with absent thymic shadow on chest X-ray. Her newborn screening test was positive for severe combined immunodeficiency (SCID). Lymphocyte subsets showed T- and B-cell deficiency, but not to the degree seen in SCID. Subsequent Immunology evaluation showed low-normal results on the mitogen stimulation test and a normal response to lymphocyte proliferation. Live vaccines are contraindicated in this patient.

Her chromosome microarray analysis was normal, which ruled out a deletion in 22q11.2 or other copy number variant/microdeletion or microduplication. Nevertheless, a repeat consult was requested to confirm these results with FISH analysis for 22q11.2. FISH testing would have been redundant given the normal chromosome microarray analysis, and it was not performed. The pattern of anomalies in this infant, which can be described as DiGeorge anomaly (rather than syndrome) were best explained by diabetic embryopathy due to the mother's preconceptional diabetes mellitus, which was poorly controlled in the first trimester.

Discussion and Counseling:

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The infant's constellation of clinical findings is best characterized as the DiGeorge anomaly (DGA). DGA is characterized by the presence of at least 2 of the following: (1) symptomatic hypocalcemia and/or parathyroid deficiency. Hypocalcemia is generally secondary to the absence or hypoplasia of the parathyroid glands (2) cellular immune deficiency or absence of part or all of the thymus. Diminished humoral immunity has also been reported, particularly in infants with DiGeorge syndrome with 22q11 deletion (3) congenital heart disease (CHD)/ cardiovascular malformation, typically conotruncal defects.

Dr. Angelo DiGeorge and colleagues at St. Christopher's Hospital for Children in Philadelphia first described this eponymous condition in 1965 in infants with hypoparathyroidism, thymic aplasia, and cellular immunodeficiency. DGA is a prototypical field defect caused by defective migration of cephalic neural crest cells into the third and fourth pharyngeal pouches during embryonic de-

velopment (Kornfeld Sj *et al.,* 2000). This can result in ectopic or absent parathyroid, thymic or parafollicular thyroid tissue:

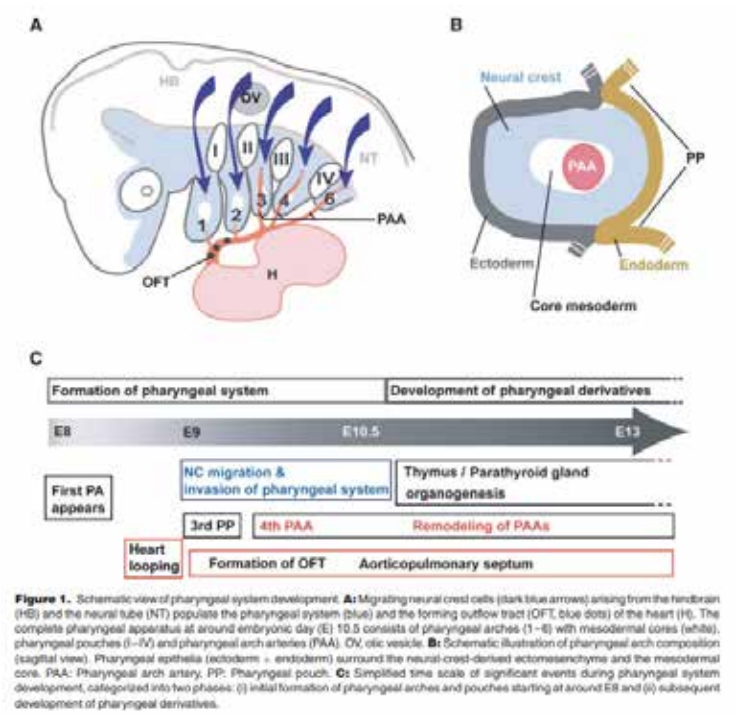

Figure 1. Schematic view of pharyngeal system development. **A:** Migrating neural crest cells (dark blue arrows) arising from the hindbrain (HB) and the neural tube (NT) populate the pharyngeal system (blue) and the forming outflow tract (OFT, blue dots) of the heart (H). The complete pharyngeal apparatus at around embryonic day (E) 10.5 consists of pharyngeal arches (1–6) with mesodermal cores (white), pharyngeal pouches (I–IV) and pharyngeal arch arteries (PAA). OV, otic vesicle. **B:** Schematic illustration of pharyngeal arch composition (sagittal view). Pharyngeal epithelia (ectoderm + endoderm) surround the neural-crest-derived ectomesenchyme and the mesodermal core. PAA: Pharyngeal arch artery, PP: Pharyngeal pouch. **C:** Simplified time scale of significant events during pharyngeal system development, categorized into two phases: (i) initial formation of pharyngeal arches and pouches starting at around E8 and (ii) subsequent development of pharyngeal derivatives.

(Wurdak H, *et al.*, 2006)

The clinical features of DiGeorge syndrome were expanded to include congenital heart disease, particularly conotruncal malformations, as well as characteristic facial dysmorphisms by circa 1972. An association between a microdeletion on chromosome 22q11.2 and DiGeorge syndrome was reported in 1981 (de la Chapelle *et al.,* 1981). These patients are now described as having 22q11.2 deletion syndrome, rather than DiGeorge syndrome, indicating the underlying etiology for their clinical features and because not all individuals with 22q11.2 deletion syndrome have all of the elements of DiGeorge syndrome.

However, some patients with DiGeorge anomaly DO NOT have a deletion on chr 22q11. 2. In a study of 64 patients who met at least 2 of the 3 criteria for DGA, the 22q11.2 deletion was detected in 55% (35/64). The other most commonly recognized etiologies for this constellation of clinical features was diabetic embryopathy (5/64) and unbalanced chromosome translocations [which would also be detected on the chromosome microarray analysis] (3/64) (Rope AF, *et al.,* 2009).

Infants of diabetic mothers are at a higher risk of birth defects. The highest window of susceptibility for fetal malformations is in the first four weeks of pregnancy, which is a strong recommendation for counseling diabetic women to optimize their diabetic control prior to conception (Castori, 2013).

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 lower the potential risk to the pregnancy: 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 (4 mg/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 (Ramanathan S, Clark RD, 2019)

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Practical Applications:

1. Be aware that poorly controlled maternal diabetes is one of the most potent human teratogens, tripling, or more the chance of birth defects.
2. Consider diabetic embryopathy when you suspect a 22q11.2 deletion, but the microarray is normal. Appreciate that although a microdeletion on chromosome 22q11 is the most common cause of DiGeorge anomaly, it is *not* the only cause. In the absence of a chr 22q11.2 deletion, maternal diabetes can cause the DiGeorge anomaly.
3. Be confident that a normal chromosome microarray test definitively rules out the deletion of chromosome 22q11.2. A FISH test for chromosome 22q11.2 is unnecessary after a normal microarray. Chromosome microarray analysis offers a higher resolution than FISH testing: it detects both small and large, typical, and atypical microdeletions on chromosome 22q11.2, and it offers more information than FISH testing by documenting the size and position of the deletion and its genomic content.
4. Counsel diabetic mothers to achieve good diabetic control prior to conception to reduce the risk for diabetic embryopathy.
    - Recommend monitoring maternal HgbA1c levels prior to gestation and early in the first trimester.
    - Counsel diabetic women of child-bearing age on the increased risk for congenital anomalies when diabetes is poorly controlled in early preg-

nancy.
- Encourage diabetic mothers to take folic acid daily starting *prior to* conception.
- 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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