

# IMAGES in PAEDIATRIC CARDIOLOGY

## Taliana N<sup>1</sup>, Said E<sup>2</sup>, Grech V<sup>1</sup>. DiGeorge phenotype in the absence of 22q11 deletion – a case report. *Images Paediatr Cardiol* 2017;19:8-9.

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### Abstract

DiGeorge syndrome is polytopic developmental field defect which is usually associated with 22q11.2 microdeletion. However, this phenotype may be caused by other conditions. We report such a case and briefly review these alternative causes for this particular phenotype.

### Introduction

DiGeorge syndrome is polytopic developmental field defect, i.e. a pattern of anomalies derived from the disturbance of a single developmental field.<sup>1</sup> In the majority of cases (over 80%), it is caused by microdeletion of 22q11.2, or less commonly, of 10p13-14.<sup>2</sup> TBX1 mutation has recently been shown to be responsible for 5 major DiGeorge phenotype manifestations, and these include abnormal facies, cardiac defects, thymic hypoplasia, velopharyngeal insufficiency of the cleft palate and parathyroid dysfunction with hypocalcemia.<sup>3</sup> Alcohol, Vitamin A, or maternal diabetes may also manifest in this phenotype.<sup>1</sup>

We report a patient with tetralogy of Fallot and thymic aplasia with negative 22q11 deletion on DNA using array CGH in a mother with insulin dependent diabetes mellitus.

### Patient

The patient is a male born at 37+2 weeks gestation by normal vaginal delivery. During pregnancy, the mother's diabetic control was poor, with an HbA<sub>1c</sub> which ranged between 54-73 mmol/mol. The parents are non-consanguineous and he has an older healthy sister.

During delivery there was mild shoulder dystocia and he needed brief resuscitation with good response. His birth weight was 3.59kg (P90). The mother's antenatal infection screen was negative. On day 2 of life, the child required transfer to NICU because of respiratory distress with non-bilious vomiting. Unconjugated hyperbilirubinaemia was also present and was treated with intravenous hydration. A systolic murmur was noted and echocardiography demonstrated Fallot's tetralogy along with severe LVH. He also had feeding difficulties and he was fed via nasogastric tube. Transfer to a tertiary centre in London for tetralogy repair occurred at 3 months of age. An isolated left brachiocephalic artery was also noted during the procedure. Recovery was uncomplicated. Other abnormalities noted were a narrow mediastinal shadow on chest xray with 11 pairs of ribs and a hemivertebra at T9.

Lymphocyte subsets demonstrated absence of T cells. Thymic hypoplasia and impaired T cell function was diagnosed and he was commenced on fluconazole, co-trimoxazole and aciclovir for prophylaxis and intravenous immunoglobulins 4 weekly. Renal ultrasound showed right crossed fused renal ectopia. Hypocalcaemia and hypomagnesaemia were treated with intravenous calcium gluconate and magnesium sulphate respectively. PTH was <5 pg/ml and hypoparathyroidism was diagnosed. He was therefore started on calcium, vitamin D3 supplements and alfacalcidol.

Immunology review was performed due to a generalized maculopapular rash with dryness of skin, and a low T cell count was noted. The patient has now undergone thymic transplant after complete recovery from the cardiac operation.

Genetic testing was performed in view of possible 22q11 deletion syndrome. Karyotype analysis was not possible because of failure of lymphocyte culture. Therefore an array CGH was done and this did not detect any deletion or unbalanced chromosomal rearrangement.

## Discussion

The association of thymic aplasia incidentally found in association with congenital heart disease, particularly with lesions involving the outflow tract/s, will result in a diagnosis of DiGeorge syndrome, implying 22q11 microdeletion. This patient highlights the importance of genetic testing prior to parental counselling, and also serves as a cautionary tale regarding other potential causes of this phenotype.

The wide variation in the phenotype maybe be due to more than one gene defect being required to manifest the severer forms of this condition. For example, an impaired signal and receptor may be needed to produce the full phenotype. Environmental factors may also play a part. Features of DiGeorge phenotype have been described in children with clinical evidence of foetal alcohol syndrome.<sup>4</sup> Foetuses exposed to the teratogen isotretinoin (vitamin A) have also been shown to manifest diagnostic criteria of DiGeorge syndrome.<sup>5</sup> This may imply that the environmental challenge is exposing the same susceptible pathways of development that are impaired by the 22q11 deletion, and/or that an interaction between the insult and genotype may be the cause.<sup>2</sup>

It is also important to watch out for other manifestations of diabetic teratogenicity in patients in whom DiGeorge syndrome is caused by diabetes in pregnancy, since these lesions are varied and legion, as summarised in Castori's review of diabetic embryopathy.<sup>6</sup>

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