Case Report

A newborn with 22q11.2 deletion without phenotypical features of Di George syndrome

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ABSTRACT

DiGeorge syndrome is a congenital primary immunodeficiency disorder resulting from failure of appropriate development of the third and fourth pharyngeal pouches during embryonic phase of development. DiGeorge syndrome usually presents with a clinical triad of immunodeficiency, congenital cardiac defects and hypocalcemia due to hypoparathyroidism. Here, we report a case of DiGeorge syndrome in a neonate with no associated facial dysmorphism and typical phenotype but initially presenting with apnea and suspected septic shock. Subsequent laboratory findings, clinical imaging and molecular genetic testing helped us to reach the diagnosis.

KEYWORDS

DiGeorge syndrome, Hypocalcemia, Immunodeficiency, Genetic testing

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INTRODUCTION

DiGeorge syndrome is a congenital primary immunodeficiency disorder resulting from failure of appropriate development of the third and fourth pharyngeal pouches during embryonic phase of development.1 DiGeorge syndrome usually presents with a clinical triad of immunodeficiency mainly due to thymic aplasia or hypoplasia, congenital cardiac defects and hypocalcemia due to hypoparathyroidism but can have varied clinical presentations in form of abnormal facies, recurrent infections, developmental delay, palatal, renal and gastrointestinal abnormalities.1,2 Microdeletion of chromosome 22q11.2 is the commonest chromosomal abnormality associated with DiGeorge syndrome, with estimated prevalence rate of 1 in 4000 live births.1,2,3 Due to variable presentations in association with DiGeorge syndrome, it can present as a challenging clinical enigma in regard to its diagnosis and related management.

CASE

A preterm female baby born to a second gravida, hypothyroid mother; with non-consanguineous marriage at 35 weeks gestational age was delivered via Caesarian section weighing 1900 grams and APGAR score of 6/10 and 8/10 at 1 and 5 minutes respectively. She had a 9 year old elder sibling who was healthy. The baby was referred to our centre at around 24 hours of age with complain of respiratory distress since birth, multiple episodes of apnea and suspected septic shock. On physical examination, high arched palate and clinodactyly was present. Pansystolic murmur was present on auscultation and baby had truncal hypotonia at presentation.

Baby was initially started on non invasive positive pressure ventilation and managed in accordance with neonatal shock algorithm with inotropic support of dopamine and dobutamine till 3rd day of life. Blood workup at presentation revealed hypocalcemia (serum calcium 6 mg/dl), which was corrected initially with intravenous calcium gluconate.

Initial chest X-ray showed apparently normal lung fields with absent thymus (Figure 1). Echocardiography done on 2nd day of life showed features of complex congenital heart disease with ventricular septal defect (VSD) with pulmonic stenosis with aberrant left subclavian artery and suspected vascular ring. Hence, computed tomography (CT) angiogram of chest was done on 11th day of life which revealed right sided aortic arch with aberrant left subclavian artery, VSD and also confirmed absence of thymus gland (Figure 2). The CT scan of chest also revealed bilateral consolidation of lungs.

Further investigations in view of hypocalcemia revealed hypovitaminosis D in both mother and baby (vitamin D level <5 nanogram/ml in mother and 14 nanogram/ml in baby). Baby was further managed with oral vitamin D, oral calcium and oral calcitriol.

In the background of hypocalcemia, congenital athymia and complex congenital heart disease, congenital immunodeficiency was suspected. Fluorescent In Situ Hybridization (FISH) test was done which was positive for Di George (Del 22q11.2) syndrome. Immunodeficiency panel showed hypogammaglobulinemia [low immunoglobulin G IgG 4.9 g/L (Normal 7-16 g/L) and low immunoglobulin A IgA <0.5 g/L (Normal 0.7-4 g/L)]. Lymphocyte subset panel however were within normal limit [Absolute CD3 2596 cells/microL (Normal 1035-4493 cells/microL); Absolute CD4 1880 cells/microL(Normal 582-2045 cells/microL); Absolute CD8 683 cells/microL (Normal 405-2615 cells/microL); Absolute CD19 965 cells/microL (Normal 115-1117 cells/microL); Absolute CD16+CD56: 1028 cells/microL (Normal 78-774 cells/microL); CD45 5938 cells/microL, CD4/CD8 ratio: 2.75 (Normal 0.6-2.4)].

As baby had respiratory distress even after treatment with broad spectrum intravenous antibiotics for lung consolidation and chest physiotherapy, in view of radiological evidence of pulmonary congestion, baby was also treated for congestive cardiac failure with diuretics and digoxin therapy after which respiratory distress subsided. Supplemental oxygen was finally discontinued at 22nd day of life. Prophylactic oral co-trimoxazole was started in view of suspected congenital immunodeficiency. Latest calcium and vitamin D prior to discharge were within normal limits (8.9mg/dl and 26.6 ng/ml respectively.) Baby was discharged home on day 27 with oral digoxin, diuretic, co-trimoxazole, calcium and multivitamin supplements with plan to be followed up by paediatric immunologist.

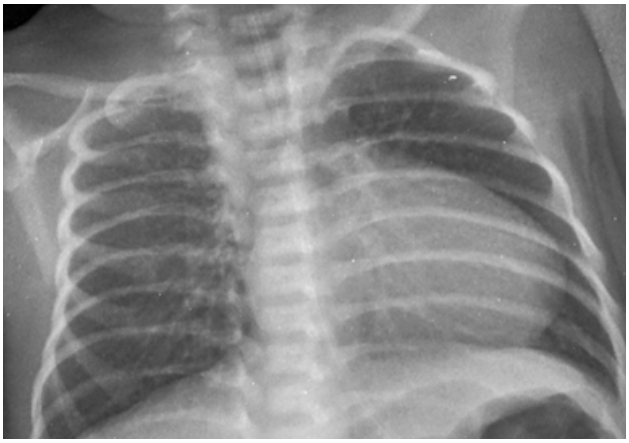


Figure 1: Chest X-ray of baby showing absent thymus

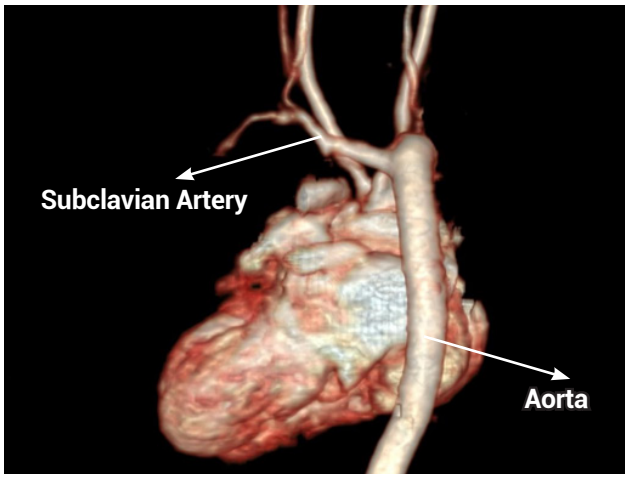
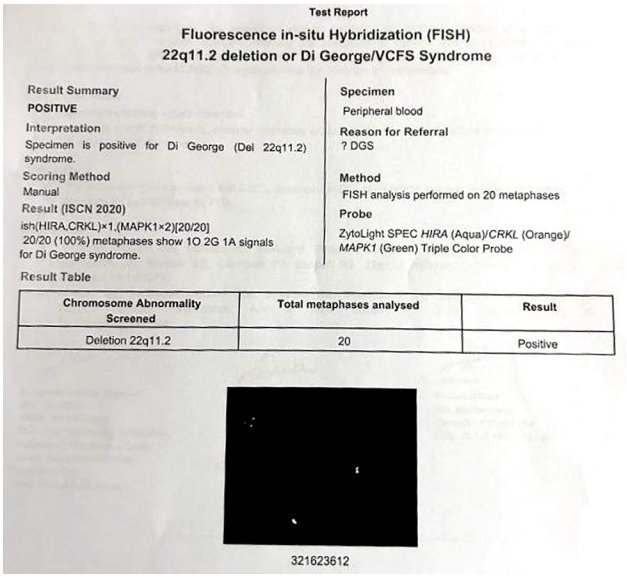


Figure 2: Volume Rendering Technique (VRT) image: posterior view in CT angiogram of chest showing right sided aortic arch with aberrant left subclavian artery



Test Report

Fluorescence in-situ Hybridization (FISH)
22q11.2 deletion or Di George/VCFS Syndrome

Result Summary
POSITIVE

Interpretation
Specimen is positive for Di George (Del 22q11.2) syndrome.

Scoring Method
Manual

Result (ISCN 2020)
ish(HIRA,CRKL)×1,(MAPK1×2)[20/20]
20/20 (100%) metaphases show 1O 2G 1A signals for Di George syndrome.

Specimen
Peripheral blood

Reason for Referral
? DGS

Method
FISH analysis performed on 20 metaphases

Probe
ZytoLight SPEC *HIRA* (Aqua)/*CRKL* (Orange)/ *MAPK1* (Green) Triple Color Probe

Result Table

Chromosome Abnormality Screened	Total metaphases analysed	Result
Deletion 22q11.2	20	Positive

321623612

Figure 3: Fluorescent In Situ Hybridization report of the baby showing positive result for Di George (Del 22q11.2) syndrome

RESULTS

Primary immunodeficiency disorders are considered rare diseases with prevalence ranging from 1:8500 to 1:1000000 in general population.4 DiGeorge syndrome being one of the most common immunodeficiency disorders, has a prevalence rate of around 1 in 4000 live births.3With a variable phenotypic presentations, this condition is most commonly caused by a microdeletion of chromosome 22q11.2. 1,2,3

In this case, the neonate presented with multiple episodes of apnea requiring non invasive ventilation support and shock requiring inotropic support. On examination, baby had pansysytolic murmur and severe hypocalcemia which was the most likely cause for apnea in this baby. Hypocalcemia is reported in upto 60-80% of cases in Di George syndrome.5,6

Interestingly, this baby did not have any classical phenotypical features generally associated with Di George syndrome. The apparent absence of thymus gland in the chest X-ray in association with hypocalcemia and congenital structural heart defect led to the suspicion of Di George syndrome in this patient. Many research articles have shown cardiac defects similar to our patient, such as ventricular septal defect, right sided aortic arch and abnormal origin of subclavian artery.7 Maternal blood workup showed severe hypovitaminosis D in our patient, which might also have contributed to severe symptomatic hypocalcemia in this patient. Our patient had decreased level of immunoglobulin G and immunoglobulin A, as similar to shown by many studies.8,9,10The diagnosis of DiGeorge syndrome was confirmed by FISH test showing deletion of chromosome 22q11.2, which remain cornerstone in diagnosis of DiGeorge syndrome.1,9,11 This case highlights the need to have high index of suspicion for Di George syndrome in infants with severe hypocalcemia and congenital cardiac defect even in absence of typical phenotype.

CONCLUSION

Prompt clinical suspicion and relevant investigations are needed in patients to diagnose congenital immunodeficiency syndrome such as DiGeorge syndrome as typical phenotypic features may not always be present as in this case. Genetic test such as FISH test remains the gold standard for diagnosis.

Abbreviations

VSD Ventricular septal defect

CT Computed Tomography

FISH Fluorescent In Situ Hybridization

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