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"FISHed" out the diagnosis: A case of DiGeorge syndrome

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ABSTRACT

Our patient presented with congenital heart disease (CHD: Tetralogy of Fallot), hypocalcemia, hypoparathyroidism, and facial dysmorphisms. Suspecting DiGeorge syndrome (DGS), a fluorescence *in situ* hybridization (FISH) analysis for 22q11.2 deletion was made. The child had a hemizygous deletion in the 22q11.2 region, diagnostic of DGS. Unfortunately, the patient succumbed to the heart disease. DGS is the most common microdeletion syndrome, and probably underrecognized due to the varied manifestations. This case stresses the importance of a detailed physical examination and a high index of suspicion for diagnosing this genetic condition. Timely diagnosis can help manage and monitor these patients better and also offer prenatal diagnosis in the next pregnancy.

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KEY WORDS: Child, congenital heart disease (CHD), DiGeorge syndrome (DGS), dysmorphism, genetic counseling, microdeletion

Case Details

Our patient was an 8-month-old male child of Indian origin and the first issue of a nonconsanguineous marriage. He presented to our center with the complaints of cough, cold, progressively increasing breathlessness, and refusal to feed over the past 3 days. Past history was elicited that the child was a full-term baby weighing 2.4 kg. His important clinical course is summarized in Table 1. On presentation to us, he had tachycardia (160 beats per minute), tachypnea (64 breaths per minute), capillary refill time of 3 s, and blood pressure of 76/60 mmHg in the right arm supine position. The child had increased work of breathing, as evidenced by the subcostal and intercostal retractions. Cardiac examination revealed a pansystolic murmur (grade III), in the third and fourth intercostal spaces. Auscultation of both the lung fields revealed bilateral crepitations with equal air entry bilaterally. The liver was not palpable. His weight, length, and head circumference were below the third percentile for his age (weight 3.5 kg, length 61 cm, head circumference 37 cm). A closer look, however, revealed some alerting dysmorphic features in the child. He had narrow and upslanting palpebral fissures, epicanthal folds, and prominent ears [Figure 1]. He also had retrognathia and an abnormal squared nasal root.

Q1: Name some hereditary and nonhereditary conditions in which the facial dysmorphisms associated with the underlying heart disease can give a clue to the etiology of the condition.

Ans.: Table 2 elaborates the conditions in which facial dysmorphisms associated with underlying heart disease can give a clue to the etiology of the condition.[1,2]

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Table 1: Past clinical course of the patient

Age of the child	Important clinical details	Corresponding relevant investigations
Day 3	Indirect hyperbilirubinemia – Phototherapy for 3 days	D3: Total bilirubin 290 μmol/L (Direct 32.49 μmol/L)
		D4: Total bilirubin 212.04 μmol/L (Direct 29.07 μmol/L)
		D5: Total bilirubin 160.74 μmol/L (Direct 17.1 μmol/L)
Day 4	1 episode of tonic–clonic seizure lasting for 5 min	HGT=1.11 mmol/L
		Serum calcium
		PCV high (partial exchange on the same day)
		CBC: TLC −13.4×10⁹/L (DLC – polymorphs 72%, lymphocytes 28%, ANC 9.64×10⁹/L, ALC 3.75×10⁹/L)
		Blood culture: Sterile
Day 6	In view of perioral cyanosis, 2D echo done	2D echo TOF with PS and a large subaortic VSD
Discharged from NICU on day 8 of life. Advised oral calcium supplementation (100 mg per kg per day) and oral propranolol (1 mg per kg per day) (On discharge serum calcium 2.275 mmol/L)		
5 months	Underwent a right ventricular outflow tract transannular patch repair, leaving the VSD unrepaired	Preoperative serum calcium 1.775 mmol/L
		Serum calcium corrected to 2.175 mmol/L over 10 days
		Serum magnesium normal
		TLC – 14.3×10⁹/L (DLC – polymorphs 18%, lymphocytes 67%. ANC 2.58×10⁹/L, ALC 9.60×10⁹/L)
6 months	In spite of compliance with oral calcium, repeat two episodes of hypocalcemic convulsion necessitating IV calcium*	Serum calcium 1.05 mmol/L
		Vitamin D normal
		CRP 277 mg/L
		CBC 17.7×10⁹/L (DLC – polymorphs 76%, lymphocytes 20%. ANC 13.45×10⁹/L, ALC 3.54×10⁹/L)
6.5 months	In spite of compliance with oral calcium, repeat two episodes of hypocalcemic convulsions (serum calcium 1 mmol/L), necessitating IV calcium*	Serum calcium 1 mmol/L
		Parathyroid hormone 0.80 pmol/L; (normal 1.59-6.89pmol/L)
		T3, T4, TSH — normal
		TLC 13×10⁹/L (DLC – polymorphs 70%, lymphocytes 30%, ANC 9.1×10⁹/L, ALC 3.9×10⁹/L)
		Blood culture — sterile
Immunized appropriately for age		

HGT = Hemoglucotest; PCV = Packed cell volume; CBC = Complete blood count; TLC = Total leucocyte counts; DLC = Differential leucocyte count; ANC = Absolute neutrophil count; ALC = Absolute lymphocyte count; CRP = C-reactive protein; TOF = Tetralogy of Fallot; PS = Pulmonary stenosis; VSD = Ventricular septal defect; *Dose of the IV calcium 2cc/kg/dose, tds for 3 days

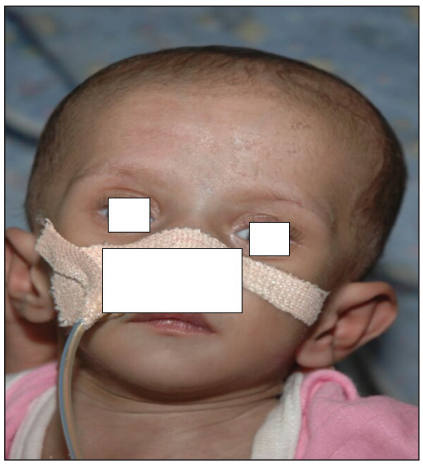

Figure 1: Facial profile of the child. Note the narrow and upslanting palpebral fissures, epicanthal folds, and prominent ears

Case details (continued): In view of the association of conotruncal cardiac anomaly, hypocalcemia with hypoparathyroidism [Table 1] in the infantile period, and typical dysmorphic facies, we were prompted to suspect DiGeorge syndrome (DGS).

Q2: What is DiGeorge syndrome?

Ans.: DGS is a 22q11.2 microdeletion syndrome, associated with the classic triad of conotruncal cardiac anomalies, hypoplastic thymus (resulting in immunodeficiencies), and hypoplasia of the parathyroid glands (resulting in hypoparathyroidism and hypocalcemia).[3] The other synonyms for DGS are 22q11.2 deletion syndrome (preferred terminology), velocardiofacial syndrome, conotruncal anomaly face syndrome, Sedlackova syndrome, and Cayler cardiofacial syndrome.[3,4] In less than 1% of all patients with DGS, there is complete athymia, resulting in severe combined immunodeficiency (SCID).[5] This is called "complete DGS;" the remaining 99% are "partial" DGS, having some thymic function preserved.[5] In our patient, repeated blood investigations failed to show lymphopenia [Table 1]. Detailed immunological tests could not be carried out in our patient. With a worldwide prevalence of between 1/2000 and 1/4000 live births, DGS is the most common microdeletion syndrome.[3,4] The actual prevalence may be higher due to high clinical expressivity, accounting for underrecognition.[3,4]

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Table 2: Conditions in which facial dysmorphisms are associated with a heart disease

Name of the syndrome/condition	Associated congenital heart disease	Associated facial dysmorphisms
Down syndrome	ECD, VSD	Brachycephaly, microcephaly, depressed nasal bridge, low-set ears, strabismus, epicanthal folds
Cri du chat syndrome	VSD, ASD, PDA	Round face, metopic ridging, hypertelorism, epicanthal folds, downslanting palpebral fissures, strabismus, downturned corners of mouth, short philtrum, micrognathia, low-set poorly formed ears, facial asymmetry
Alagille syndrome	Peripheral pulmonary artery stenosis with/ without other complex cardiovascular anomalies	Deep-set eyes, broad forehead, long straight nose with flattened tip, prominent chin, and small low-set malformed ears
Mucopolysaccharidosis	AR, MR, CAD	Macrocephaly, frontal prominence, coarse facies with full lips, flared nostrils, low nasal bridge, tendency toward hypertelorism, inner epicanthal folds, with or without corneal clouding, hypertrophied alveolar ridge, and gums with small misaligned teeth, enlarged tongue
Williams syndrome	Supravalvular AS, PA stenosis	Short palpebral fissures, depressed nasal bridge, epicanthal folds, periorbital fullness of subcutaneous tissues, stellate pattern in the iris, anteverted nares, long philtrum, prominent lips with open mouth
DGS	Interrupted aortic arch, truncus arteriosus, VSD, PDA, TOF	Prominent nose with squared nasal root and narrow alar base, narrow palpebral fissures, hypertelorism, hooded eyelids, deficient malar area, long face, retrognathia, microcephaly, prominent ears, asymmetric crying facies
Fetal alcohol syndrome	VSD, ASD, PDA, TOF	Mild-to-moderate microcephaly, short palpebral fissures, maxillary hypoplasia, short nose, smooth philtrum with thin and smooth upper lip
Congenital rubella syndrome	PDA, PA stenosis	Microcephaly, microphthalmia

ECD = Endocardial cushion defect; ASD = Atrial septal defect; PDA = Patent ductus arteriosus; AR = Aortic regurgitation; MR = Mitral regurgitation; CAD = Coronary artery disease; AS = Aortic stenosis; PA = Pulmonary artery; DGS = DiGeorge syndrome

Q3: How is DiGeorge syndrome caused?

Ans.: DGS is caused due to the deletion of the genes in the DiGeorge chromosomal region (DGCR) on chromosome 22q11.2, secondary to a nonallelic meiotic recombination during spermatogenesis or oogenesis.[6] A great percentage (93%) of the probands have a *de novo* deletion of 22q11.2, while some (7%) inherit the 22q11.2 deletion from a parent in an autosomal dominant fashion.[5-7] Rarely, less than 1% of the individuals with DGS have chromosomal rearrangements, such as a translocation between chromosome 22 and another autosome, involving 22q11.2.[5]

Q4: What are the clinical features of DiGeorge syndrome?

Ans.: The clinical features of DGS [Table 3], are exceedingly variable, with over 190 features described in the literature, involving almost every organ system — [3,5,8,9] thus underlining the need for sensitization among physicians and surgeons from all specialties. Of note, no phenotype occurs in 100% of the patients, as the penetrance of each clinical feature is diverse.[10] Thus, one should be wary of excluding differential of DGS solely on the basis of absence of a particular feature.[10] The presence of congenital heart disease (CHD; especially conotruncal anomalies), neonatal hypocalcemia (with hypoparathyroidism), and palatal defects can usually be picked up in the neonatal period, and should serve as red flags for early diagnosis.[3,11] Authorities in this subject recommend that, given the high frequency of DGS among individuals with conotruncal anomalies,

Table 3: Clinical features of DiGeorge syndrome

System involved	Details of the system involvement
Immune deficiency	Impaired T-cell production and function, humoral defects, selective IgA deficiency. Range of clinical presentation: Insignificant immunosuppression to (rarely) SCID
CHD	Conotruncal malformations (TOF, interrupted aortic arch, VSD, truncus arteriosus), PDA
Craniofacial	Noted in Table 2
Palate	Velopharyngeal incompetence (structural/ functional), submucous cleft, bifid uvula, cleft lip, cleft palate
Endocrinological	Hypocalcemia, hypoparathyroidism, hypothyroidism, growth hormone deficiency
Developmental delay, learning difficulties, neuropsychiatric manifestations	Delayed emergence of language, learning difficulty, autistic spectrum disorder, psychosis (mainly in adults), attention deficit disorder, anxiety
Ophthalmological	Strabismus, posterior embryotoxon, tortuous retinal vessels, anophthalmia
Skeletal abnormalities	Pre- and postaxial polydactyly, supernumerary ribs, hemivertebrae, butterfly vertebrae, craniosynostosis
Autoimmune disease	Autoimmune cytopenias, JRA, autoimmune thyroid disease
Others	Hearing loss, growth retardation, renal anomalies, seizure disorder, laryngotracheoesophageal anomalies, gastrointestinal anomalies, Bernard–Soulier syndrome, malignancies (rarely)

SCID = Severe combined immunodeficiency; CHD = Congenital heart disease; JRA = Juvenile rheumatoid arthritis

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newborns with these heart anomalies should be routinely screened with fluorescence *in situ* hybridization (FISH) for 22q11.2 deletion, once other causes (Down syndrome, trisomy 13) have been ruled out.[3,5] Other pointers for this condition, such as dysmorphisms, intellectual disability, and psychiatric disorders may appear only years later, often delaying the diagnosis.[11] An emerging area of great interest is the high predilection of psychotic disorders (including schizophrenia and bipolar disorders) in adolescents and adults with DGS (25 times higher than the general population).[12,13] Other than serving as a reminder to psychiatrists, this also underlines that pediatricians and geneticists dealing with DGS/suspected DGS should diligently excavate the psychiatric history of the pedigree in detail, along with the other relevant particulars.

Case details (continued): In view of suspected DGS, FISH was performed using TUPLE1 probes on 200 interphase nuclei and 7 metaphases of the cultured blood. All the cells analyzed showed a heterozygous deletion in the 22q11.2 region [Figures 2a and b]. This clinched the diagnosis of DGS in our patient.

Q5: What is the diagnostic modality for DiGeorge syndrome?

Ans.: The most regularly and widely used diagnostic test for detecting the 22q11.2 deletion is FISH using probes for the commonly deleted region.[5] It can pick up around 95% of all deletions causing DGS.[5] However, around 5% of the cases may require more sophisticated and costlier methods such as multiplex ligation-dependent probe amplification (MLPA) and array comparative genomic hybridization (aCGH) to detect the underlying genetic aberration.[5] The presence of a CHD in association with one or more of the following should serve as an important red flag for considering an underlying chromosomal imbalance as the possible genetic etiology: growth failure, intellectual disability, other malformations affecting a second organ, multiple anomalies, and dysmorphic features.[14] In such cases, when the conventional karyotype fails to pick up the underlying genetic condition, an aCGH can lead to increased detection of the underlying causal chromosomal imbalance.[14] The major advantage of this aCGH technique is its increased resolution, which surpasses that of conventional karyotyping by at least fivefold.[15] In an excellent study by Breckpot *et al*., 150 children with an underlying CHD and one or more of the red flags mentioned above were subjected to aCGH, after a genetic diagnosis could not be reached despite a conventional karyotype and ruling out well-defined genetic disorders. Of these 150 children, 24 (17.3%) were detected as having an underlying copy number variation (CNV), that is, a deletion or duplication, as responsible for their syndromic CHD, as detected by aCGH.[15] Some examples of the CNVs detected in this study include 1p36 deletion, 1q21.1 duplication, 8q deletion, 14q32 deletion, and 16p13.3 duplication.[15] aCGH can also diagnose, among many other CNV conditions, Williams syndrome[16] and some cases of CHARGE syndrome.[17]

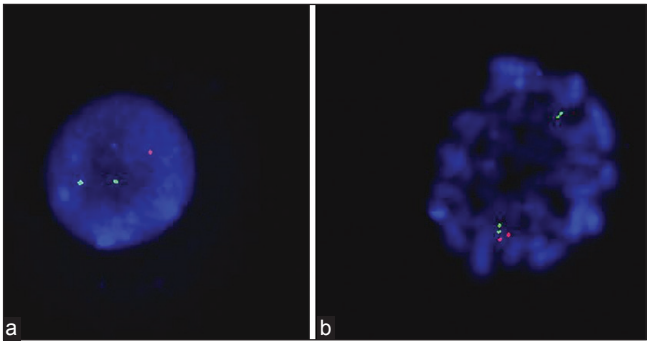

Figure 2: (a) FISH image of the patient: Interphase cell. Presence of two green signals (control ARSA probe, locus 22q13) one orange signal (TUPLE1, locus 22q11.2) denotes hemizygous deletion in the 22q11.2 region (b) FISH image of the patient: Metaphase cell, each cell has two chromatids. Presence of two pairs of green signals (control ARSA probe, locus 22q13) and only one pair of orange signals (TUPLE1 locus 22q11.2) denotes hemizygous deletion in the 22q11.2 region

Case details (continued): On admission in our center, the child had leukocytosis (total leukocyte count = 32 × 10^9/L) and radiological evidence of bronchopneumonia. His blood cultures were sterile during this stay. He was administered intravenous antibiotics for 11 days. However, the child's condition worsened on day 9, due to congestive cardiac failure precipitated by the infection. In spite of ionotropic support and mechanical ventilation, the child could not be revived and expired on day 11 of hospital stay.

Q6: Does the timely diagnosis of DGS change the management in these patients?

Ans.: Timely diagnosis of this condition can alert the treating physician about the possibility of the associated comorbities known to occur with this disease. This in turn can help to develop a surveillance plan for these patients.[4,5] Acute management in neonates and during infancy is mainly focused on the evaluation and treatment of hypocalcemia and the underlying CHD as in our case.[3,4,5] Proactive prevention of the secondary complications and a watchful "system-wise" surveillance plan can go a long way in ensuring a healthy life for most of these individuals [Table 4].[4,5] Thymic transplantation in those with "complete" DGS, especially if done early, may be beneficial. However, the lack of centers performing thymic transplantation in India and the immunosuppression following the transplant make that a difficult option.[18]

Case details (continued): The parents were offered genetic counseling, the main focus being on the future risk of recurrence, as our patient was the first issue.

Q7: What genetic counseling was offered to the parents?

Ans.: Following the detection of 22q11.2 deletion in the proband, it is of vital importance to screen both the

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Table 4: Prevention of secondary complications and the system-wise surveillance in patients with DiGeorge syndrome

Prevention of secondary complications	Surveillance parameters
Avoid live vaccines in patients with lymphocyte abnormalities, especially those with severe immunodeficiencies. Reevaluation of immune status before every schedule of live vaccines. Practically, in those with mild–moderate immunodeficiencies, live vaccines are frequently given and generally well tolerated	Serum and ionized calcium Infancy — every 3-6 months Childhood — every 5 years Adolescence and adulthood — every 2 years
Irradiated blood products awaiting normalization of the immune system	TFT, CBC —— annually
Preoperative assessment — platelet number and function, cervical spine abnormalities (for anesthesia/intubation)	Immune system — evaluation at birth, and at 9-12 months. Reevaluation prior to any live vaccine
Pre- and postoperative assessment — serum calcium	
For surgical operations involving the pharynx — preoperative assessment of the carotid arteries. Pre- and postoperative — sleep studies	Ophthalmological assessment at 1-5 years
	Speech assessment to rule out velopharyngeal incompetency
	Auditory assessment — infancy and preschool
	Routine evaluation of developmental milestones, regular dental examinations (high risk of caries), and spine examination
	Routine psychological evaluation

parents for the same (using FISH or MLPA) in order to ascertain the origin of the deletion, sporadic or inherited.[19] This information can impact the risk of recurrence and thus the genetic counseling offered.[19] If either parent is detected with the deletion, then the risk of recurrence in the next pregnancy is 50% irrespective of the sex of the child (autosomal dominant inheritance).[3,5,20] However, if the parents of an individual with 22q11.2DS have normal studies, the risk of recurrence in the subsequent pregnancy is low, though greater than that of the general population.[3,5,20] This is due to the possibility of germline or low-level somatic mosaicism in the parents.[3,5,20] McDonald-McGinn *et al.* report retrospectively detecting 30 relatives of probands having a deletion in the 22q 11.2 region, following a diagnosis in the proband. Of note, only 32% of the adults and 55% of the children in this case series ever had any major medical problems warranting care.[19] Thus, the absence of obvious clinical features should not be a reason to exclude the screening for the 22q11.2 deletion in the parents, if their child has been proven to carry the same. Unfortunately, in our case the parents were unwilling to investigate themselves further. In the scenario of one child having DGS, prenatal testing by FISH or MLPA can be offered in the next pregnancy, using fetal cells obtained by chorionic villus sampling (10-13 weeks of gestation) or amniotic fluid analysis (15-18 weeks of gestation.)[5] In pregnancies without any family history of the disorder, the sonographic markers that should prompt one to request for prenatal diagnosis are: CHD (especially conotruncal anomalies) and/or cleft lip and/or cleft palate, congenital diaphragmatic hernia, umbilical or inguinal hernia, tracheoesophageal fistula/esophageal atresia/laryngeal atresia, polydactyly, craniosynostosis, polymicrogyria, and renal anomalies.[3,5]

Q8: What is the long-term prognosis in these patients?

Ans.: The prognosis for patients with DGS depends mainly on whether the DGS is partial or complete and on the severity of the underlying cardiac defect.[3,5,18] Most children with complete DGS who do not undergo a thymic transplant usually die in infancy.[18] In contrast, the overall mortality rate in children with partial DGS is reported to be <10%, most of them due to the underlying heart disease.[3,5,21] However, if the child with an underlying heart disease has a successful repair, then the prognosis may be much better, the majority of the immunological problems settling with time.[3] The endocrinological problems, too, do not tend to be devastating, most of them being treatable.[3] Learning disabilities, speech issues, and psychiatric manifestations respond well if remedial and supportive therapy is begun early.[3]

Conclusion

DGS is the most common microdeletion syndrome, with a notoriety of being clinically varied. A high index of suspicion is necessary to diagnose DGS. Timely diagnosis aids better management, more holistic counseling, and the opportunity for prenatal diagnosis in a subsequent pregnancy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

Dr. Milind Tullu works as the Associate Editor for the JPGM and Dr. Mukesh Agrawal is an Editorial Board Member for JPGM.

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