

DiGeorge syndrome presenting with seizure in neonatal period: a case report

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ABSTRACT

DiGeorge syndrome is caused by a micro-deletion of chromosome 22q11.2 that disrupts development of the third and fourth pharyngeal pouches during early embryogenesis. Other structures forming at the same period are also frequently affected. So, the phenotypic spectrum shows a wide variability. In this case report, we describe a 1-month and 24-day old male child who presented with history of recurrent afebrile seizure and noisy breathing since early neonatal period. He had history of repeated chest infections. On examination, patient had stridor, facial dysmorphism, pectus excavatum and clinical features of pneumonia. Investigations revealed hypocalcaemia, hypoparathyroidism, consolidation on X-ray chest and cellular immunodeficiency. Echocardiography findings were normal. Fluorescent in situ hybridization (FISH) was performed which confirmed the diagnosis 22q11.2 deletion.

Key words: DiGeorge syndrome, seizure, persistent hypocalcaemia, cellular immunodeficiency.

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INTRODUCTION

DiGeorge syndrome or 22q11.2 deletion syndrome (22q11.2 DS) is the most common chromosomal microdeletion disorder.¹ It was first described by Dr. Angelo DiGeorge in 1965, who reported an infant with absence of the thymus (thymic aplasia), parathyroid glands (hypoparathyroidism) and congenital heart disease (CHD), especially involving the outflow tract.² It is usually diagnosed at early infancy and often first

suggested by hypocalcaemic seizures during neonatal period.³ Here, we present a case of DiGeorge syndrome, who presented with recurrent afebrile seizures, persistent hypocalcaemia and repeated chest infections since early neonatal period. Creating further awareness and highlighting the importance of early diagnosis and management of this rare disorder are necessary to improve the quality of life of such cases.

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CASE REPORT

A 1-month and 24-day old male child, first issue of his non-cosanguineous parents, presented with history of recurrent afebrile seizure and stridor since 6 days of age. No other family members had similar history. His birth event was uneventful. At birth his weight, length and occipitofrontal circumference (OFC) was age appropriate. At 1-month and 15-days of age, he required hospitalization due to recurrent episodes of afebrile seizure and choking following feeding. Investigations revealed hypocalcaemia, hypoparathyroidism and aspiration pneumonia. For these, he was treated with supportive measures. He was referred to our hospital for evaluation of persistent hypocalcaemia.

On admission, patient was afebrile, had stridor and facial dysmorphism (low set ear, micrognathia) (Figure 1), deviation of angle of mouth towards right during crying and pectus excavatum (Figure 2). There was

suprasternal, intercostal, subcostal recession and tachypnoea. Crepitations were present in both lung fields. There was no murmur. Anthropometry revealed weight 3.2 kg (between 3rd and 5th centile), OFC 38 cm (on 10th centile), length 55 cm (on 50th centile).



Figure 1 Facial dysmorphism (low set ear, micrognathia) of the child with DiGeorge syndrome



Figure 2 Pectus excavatum of the child with DiGeorge Syndrome

Investigations revealed hypocalcaemia, hypomagnesemia, hyperphosphataemia and hypoparathyroidism. His vitamin D level was also low (Table I). Maternal vitamin D status was not done. A narrow superior mediastinum was seen on chest X-ray with bilateral opacity (Figure 3). Patient's blood counts, serum electrolyte, thyroid function test were normal. Echocardiogram showed normal findings. Ultrasonography (USG) of brain and abdomen revealed no abnormality.

Table I Laboratory parameters of the patient with DiGeorge syndrome

Parameters	Patient value	Reference value
Serum calcium	3.86 mg/dl	8.4-10.4 mg/dl
Serum magnesium	0.43 mmol/L	0.7-1.05 mmol/L
Serum phosphate	8.2 mg/dl	2.4-5.9 mg/dl
Serum parathormone	2.00 pg/ml	7-53 pg/ml
Serum vitamin D	19.38 ng/ml	30-40 ng/ml



Figure 3 Narrow anterior mediastinum of the child with DiGeorge syndrome

Fluorescent in situ hybridization (FISH) method showed 22q11.2 deletion that confirmed the diagnosis of DiGeorge syndrome (Figure 4). Parenteral genetic analysis was not done. Alongside primary immunodeficiency panel (PID panel) was done which revealed low level of lymphocytes count. Absolute count of CD3+ T cells and its subset CD4+ cells, CD8+ T cells were grossly reduced. There was borderline low level of immunoglobulin (Table II). The overall immunophenotypic findings were also suggestive of DiGeorge syndrome.



Figure 4 Fluorescent in situ hybridization analysis showed 22q11.2 deletion in the child with DiGeorge Syndrome

Table II Primary immunodeficiency panel and immunoglobulin reports of the patient with positive findings

Parameters	Patient value	Reference value
	Cell count	Cell count
	(percentage)	(percentage)
	Cells/uL (%)	Cells/uL (%)
Lymphocytes	2548 (46)	3320-7006 (upto 61)
CD3+ T cells	382 (15)	2284-4776 (51.8-74.2)
CD4+ T cells	217 (8.5)	1523-3472 (34.9-53.1)
CD8+ T cells	96 (3.8)	524-1583 (12.8-27.1)
Parameters	Patient value	Reference value
Immunoglobulin G(IgG)	6.13 g/l	7-16 g/l
Immunoglobulin M (IgM)	0.71 g/l	0.4-2.3 g/l
Immunoglobulin A (IgA)	0.534 g/l	0.7-4.0 g/l

He was treated with oxygen inhalation, injectable antibiotics, injectable calcium gluconate, cap. calcitriol and injectable magnesium sulphate. Injectable phenobarbitone was needed due to episode of convulsion after admission. Patient was discharged at 2 months and 18 days of age with oral calcium and calcitriol. During discharge his serum calcium, magnesium and phosphate levels were within normal limits and he had no seizure. Parents were counseled regarding disease process, treatment and prognosis. They were advised to come for follow-up regularly.

Patient was well up to 4 months of age. Then, he got admitted for fever, cough and respiratory distress. Investigations revealed anaemia (Hb 7.8 gm/dl), hypocalcaemia (S. Ca 5.4 mg/dl), hypomagnesaemia (S. Mg 0.45 mmol/L) and consolidation on both lung fields in chest X-ray. Blood culture revealed growth of *non-albicans candida*. He was managed with continuous positive airway pressure (CPAP) ventilation, injectable antibiotics, antifungal, injectable calcium gluconate, calcitriol, immunoglobulin and irradiated whole blood transfusion. He was discharged after 2 weeks with oral calcium, calcitriol, magnesium, prophylactic sulfamethoxazole-trimethoprim combination and itraconazole. At 1 year and 3 months of age, he was admitted for generalized tonic-clonic seizure. At that time, he had no fever and investigation revealed S.Ca level was 8.1 mg/dl. Electroencephalogram (EEG) was done and found normal. Patient was managed with injectable phenobarbitone at hospital and after control of seizure he was discharged at home with oral phenobarbitone along with ongoing medications. Now patient is 1 year and 6 months of age, doing well with these supportive measures. He has mild motor delay and moderate speech delay but he is playful and interactive. He is seen regularly by multidisciplinary team, caring for his various problems.

DISCUSSION

DiGeorge syndrome has a wide phenotypic spectrum and an estimated incidence is 1 in 4000 live births.⁴ In 90% of cases, it occurs due to sporadic de-novo deletions of 22q11.2 and only 10% inherits as autosomal dominant trait.¹ Familial cases have also been described. It affects male and female equally.⁵ In our case, there was no family history of similar type of illness. So, most likely it sporadic case. This deletion results in disruption of development of 3rd and 4th pharyngeal pouches

during early embryogenesis with disruption of other associated organ system leading to widespread heterogeneous phenotypic expression. These variable presentations are seen even among the family members with same mutations.⁵ Thus early diagnosis may be difficult. Hypocalcaemia (70%), absent thymus (70%) and congenital heart defects (75%) are the cardinal features of DiGeorge syndrome.⁶ Neonatal hypocalcemia occurs in 60% of affected patients with this syndrome.⁷ The hypocalcemia may be of variable severity and presents as recurrent seizure and/or recurrent croup attacks at different ages.⁸ As neonatal hypocalcaemia has so many maternal and neonatal causes, so in the absence of congenital heart defects suspicion towards DiGeorge syndrome may not be the first priority. In this case report our patient had hypocalcaemia induced recurrent episode of afebrile seizure and croup attack without any congenital heart defects. Later, patient developed unprovoked seizures in the absence of hypocalcaemia for this he needed antiepileptic drugs (AED). In 22q11.2 DS around 7% patients may develop seizure disorder and needs AED.⁹

Typical dysmorphic facies is another important clinical finding. Our patient had only micrognathia and low set ear without any palatal involvement. Usually 17% patients with DiGeorge syndrome have palatal involvement.⁶ Congenital asymmetric crying facies, caused by the absence or hypoplasia of the depressor anguli oris muscle on one side of the mouth, has also been reported in 22q11 DS¹⁰, which was present in our patient.

Patients with DiGeorge Syndrome have a variable degree of immunodeficiency due to an underdeveloped or absent thymus. T cell immunodeficiency is of major significance in patients with “complete” DiGeorge syndrome and aplasia of the thymus, where affected patients need immune reconstitution, usually with bone marrow transplantation or thymic transplants. This is fortunately rare, occurring in less than 1% of reported cases.¹¹ Infections are often problematic across the lifespan of an individual with complete DiGeorge syndrome. Unfortunately our case was one of those having T cell immunodeficiency.

For the majority of patients with DiGeorge syndrome who are not severely immunodeficient, prophylaxis is often not necessary. Antimicrobial (antibiotic and

antifungal) prophylaxis is recommended in patients who have significant defect in CD4+ cells and in case of complete DiGeorge syndrome with severe combined immunodeficiency (SCID) like features. These patients are at risk of opportunistic infections such as *Pneumocystis jiroveci*, *Cytomegalovirus* and sometimes fungus. So, they should be treated with prophylactic broad spectrum antibiotics. Antifungal should be considered when there is invasive fungal infection.¹² Most recommended antibiotic is sulfamethoxazole-trimethoprim combination. Prophylaxis should be discontinued once CD4+ cell counts reach normal values.¹²

Our patient had repeated attacks of pneumonia, invasive fungal infection and grossly reduced CD4+ cells. So, he is getting sulfamethoxazole-trimethoprim combination and itraconazole prophylaxis. Now patient is doing well with these prophylaxis and attack of pneumonia is also decreased.

Immunoglobulin replacement should be offered to those with demonstrated humoral defects. And these sorts of patients who have cellular immunodeficiency should receive irradiated or leucocyte depleted blood when needed.⁵ At four months of age, our patient was admitted with severe systemic infection and developed anaemia. He was treated with irradiated blood transfusion and intravenous immunoglobulin along with other supportive measures.

Limited studies have been done on the use of live viral vaccines in DiGeorge population. Few studies showed adverse events following live vaccination in DiGeorge patients not higher than those of the general population. But in those studies, the total CD4+ T cell counts were significantly higher than the CD4+ T cell counts of our patient.¹³ There are also documented reports of severe life threatening adverse effects following immunization with live vaccine in case of DiGeorge syndrome. The Advisory Committee on Immunization Practices (ACIP) revised their recommendations and advised withholding measles, mumps and rubella (MMR) vaccination for severely immunocompromised persons, defined as a CD4 T lymphocyte count of less than 750 cells/uL or less than 15% of total lymphocytes for children less than 1 year of age.¹³ Our patient had only 8% (217 cells/uL) CD4+ cell of total lymphocytes when he was < 1 year of age. As there is limited data for administration of live

vaccine in patients with DiGeorge syndrome, we advised not to give live vaccines, although before presenting to us our patient received Bacille Calmette-Guérin vaccine (BCG) and first dose of pentavalent vaccine of Expanded Programme on Immunization (EPI) schedule including live vaccine. Response of BCG vaccine was well and there were no documented side effects following vaccination.

Premature mortality is about 4% of all infants with 22q11.2 DiGeorge syndrome. Cardiac defects, hypocalcaemia and airway malacia are risk factors for early death, with median age at death of 3–4 months.¹⁴ Major morbidities are associated with developmental and learning disabilities (80%) which can be managed by early interventions. Our patient also had mild motor delay and speech delay, he is regularly seen by our child development centre (CDC) team. As the patient does not have any cardiac defect, airway getting matured, hypocalcaemia is controlled with supplements. So, if the rate of infection is decreased with antimicrobial prophylaxis then we hope his better prognosis than usual DiGeorge syndrome patient.

Prenatal genetic counseling should be offered for couples in whom one partner has the 22q11.2 deletion with a 50% recurrence risk.⁵ We have plan to offer his parents for genetic diagnosis as well as counseling regarding future pregnancy.

Conclusions

Early diagnosis and combined management through multidisciplinary and coordinated care plan improves the quality of life of a patient with this rare syndrome. To confirm the diagnosis availability of genetic analysis in our country is one of the desirable issues now-a-days.

Authors' contribution: NB was involved in drafting and manuscript writing which was critically revised and guided by FM. All have authors were involved in patient management. All authors read and approved the final manuscript for submission.

Consent: Taken from parents for this publication.

Conflicts of interest: Nothing to declare.

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