CASE REPORT

Riddles of the Newborn: DiGeorge Syndrome, Imperforate Anus, and the Enigma of Recurrent Infections.

Sakinah MR[1], Mohd Aizuddin AR[2], Maznun MJ[3], Nurul Najmi MI[4].

[1]Kesihatan Bandar Bera 32, Jalan Tementi, Sebertak,28300 Bera, Pahang, Malaysia
[2]Department of Family Medicine, Kulliyyah of Medicine, International Islamic University Malaysia, Bandar Indera Mahkota Campus, 25200 Kuantan, Pahang, Malaysia
[3]Klinik Kesihatan Triang, Taman Daro, 28300 Triang, Bera, Pahang, Malaysia
[4]Klinik Kesihatan Padang Luas, 28200 Bera, Pahang, Malaysia

Corresponding Author
Mohd Aizuddin Abd Rahman
Department of Family Medicine
Kulliyyah of Medicine, International Islamic University Malaysia,
Bandar Indera Mahkota Campus,25200 Kuantan, Pahang, Malaysia.
Email: draizu@iitm.edu.my

Submitted: 16/01/2024. Revised edition: 20/03/2024. Accepted: 21/03/2024. Published online: 01/06/2024.

Abstract

DiGeorge syndrome, also recognized as 22q11.2 deletion syndrome, is a prevalent chromosomal microdeletion disorder characterized by atypical development of the third and fourth pharyngeal pouches, with associated consequences for concurrently developing structures. The resulting phenotypic spectrum is notably diverse. This case report depicts a 3-month-old male infant presenting with imperforate anus and recurrent infections. Prenatal ultrasonography showed congenital cardiac defects, mild bilateral hydronephrosis, and polyhydramnios without the inclusion of amniocentesis in the diagnostic process. Clinical examination revealed facial dysmorphism and imperforate anus. Further investigations detected hypocalcaemia, hypoparathyroidism, and cellular immunodeficiency. Echocardiography confirmed the presence of truncus arteriosus. The baby encountered a stormy period in the Neonatal Intensive Care Unit (NICU), complicated by recurrent infections, cardiac failure, and infantile erythroderma, ultimately leading to *Pseudomonas aeruginosa* septicemic shock. A Fluorescence In Situ Hybridization (FISH) analysis confirmed the presence of a 22q11.2 deletion, establishing the diagnosis of DiGeorge syndrome in this case. The multifaceted clinical presentation underscores the complexity of this syndrome, emphasising the importance of comprehensive evaluation and timely diagnosis for effective management and care.

Keywords: *DiGeorge syndrome; 21q11.2 deletion syndrome; facial dysmorphism; hypocalcaemia.*

Introduction

DiGeorge syndrome is an immune system disorder with pharyngeal pouch abnormalities and a variety of symptoms [1]. It is caused by chromosome 22q11.2 deletion. In 1965, Dr. Angelo DiGeorge noticed a newborn with underdeveloped thymus, parathyroid glands, and congenital cardiac disease, notably impacting the outflow tract, and first described this syndrome [2]. Since infections and congenital heart abnormalities are common in children, they are usually discovered early [2]. DiGeorge syndrome in an infant with imperforate anus and recurrent infections is addressed here. Increasing awareness and emphasising early detection and treatment of this rare disease improves the well-being of those affected.

Case study

A 2.4kg 3-month-old child was born full term. His mother had gestational diabetes mellitus and needed 26 insulin units daily. Prenatal ultrasound revealed atrial septal defect (ASD), polyhydramnios and mild bilateral renal hypertrophy. In view of the antenatal abnormalities detected, he was referred to the paediatric team for evaluation and further management.

Upon examination, he had a downward slanting palpebral fissure, low-set ears, pre-auricular skin tag, a skin tag on the left lower cheek, long and slender fingers, micrognathia, imperforate anus, and a sacral dimple 3 cm from the imperforate anus. All other systemic examinations were unremarkable. He was then referred to the surgical team for imperforate anus and had left transverse colostomy for anorectal malformation on day 3 of life. Due to the dysmorphism, chromosomal testing and fluorescence in situ hybridization (FISH) for DiGeorge syndrome were ordered. He had normal chromosomal karyotyping but a positive diagnosis for DiGeorge syndrome. A paediatric consultant cardiologist identified truncus arteriosus (Type A3, Van Praagh Classification) and notable aortopulmonary collateral arteries through echocardiography. The child was tachycardic and tachypneic, under ventilator support. Anti-failure medication was administered to treat signs of failure associated with truncus arteriosus.

At two weeks of life, he was noted to have persistent hypocalcaemia. The serum phosphate was high and inversely, the calcium level was low. Otherwise, serum alkaline phosphatase was normal. The serum parathyroid hormone (PTH) level was measured at 1.6 pg/mL. Otherwise, he had no jitteriness, fits or spasms. The paediatric endocrine team prescribed calcium gluconate infusions and supplements to treat the newborn's hypocalcaemia.

Throughout his stay in the Neonatal Intensive Care Unit (NICU), he faced complications such as infections, heart failure, and infantile erythroderma. At three months old, he succumbed to septicemic shock following *Pseudomonas aeruginosa* bacteraemia, with underlying DiGeorge syndrome and primary immune insufficiency.

Discussion

DiGeorge syndrome manifests in approximately 1 in 4000 live births, displaying a spectrum of multiple abnormalities (2). In the majority (90%) of cases, spontaneous de-novo deletions of 22q11.2 are the causative factor, while the remaining 10% are linked to autosomal dominant inheritance. The syndrome affects both genders, and there have been documented instances of familial cases. However, in the absence of any familial history of the condition, it suggests that the disease occurred sporadically. The presence of a hemizygous 22q11.2 deletion contributes to a diverse range of phenotypes associated with DiGeorge syndrome. Other differential diagnoses under 22q11.2 microdeletion syndrome include Velo-Cardio-Facial and Shprintzen syndromes,

whose disorders represent different manifestations of the same genetic defect [3].

The typical manifestations of DiGeorge syndrome include cardiac abnormalities, thymic hypoplasia, and hypocalcaemia [4]. Many of these patients have low T lymphocyte counts (4). Newborn hypocalcemia is prevalent, occurring in approximately 60% of cases, as exemplified in this particular case [5]. Another distinctive feature is the presence of characteristic facial features. A down-slanting palpebral fissure, lower set ears, retrognathia, micrognathia, and a lower ear without palate involvement were observed in the patient. Palatal involvement affects 17% of DiGeorge syndrome patients [5].

Pregnancies carrying a risk for the 22q11.2 deletion often exhibit abnormal fetal ultrasound results and a family history of the syndrome [6]. Features such as cleft palate, polyhydramnios, and abnormalities in renal, skeletal, and cardiac structures may raise suspicion [7]. In the presented case, the patient displayed distinctive ultrasonographic features, and no family history of the disease. Notably, the majority of 22q11.2 deletion syndrome cases involve congenital heart disease [2]. As routine ultrasound techniques advance, more cardiac defects are expected to be identified during prenatal diagnosis. Although a conclusive answer may not always be reached, ongoing advancements in ultrasonography and increased awareness among physicians regarding the presentation of 22q11.2 deletion syndrome are anticipated to elevate the demand for prenatal diagnosis.

When foetal echocardiography identifies a cardiac abnormality, FISH is recommended for confirmation. Although ultrasound and foetal echocardiography are not diagnostic on their own, FISH and cytogenetic studies serve to confirm any suspected abnormalities. FISH is particularly effective for detecting the 22q11.2 deletion [7]. Early prenatal diagnosis, especially through efficient FISH testing, is crucial for genetic counselling. It facilitates informed pregnancy decisions and ensures optimal care for both the mother and child. The rapid and accurate detection of microdeletions, especially the 22q11.2 deletions, is a notable advantage of FISH [7]. DiGeorge Syndrome, characterized by an underdeveloped or absent thymus, leads to various immunodeficiencies.

Complete DiGeorge syndrome patients may face T cell immunodeficiency, necessitating immune reconstitution through procedures like bone marrow or thymic transplants, although this is a rare occurrence (less than 1%) (4). Those with complete DiGeorge syndrome often battle infections throughout their lives, with susceptibility to infections such as *Pneumocystis jirovecii*, *cytomegalovirus,* and fungal infections due to their compromised immune systems [1]. Prophylactic use of broad-spectrum antibiotics is recommended to prevent infections. Invasive fungal infections require antifungal treatment, and the presented case involved the use of imipenem, cefepime, and fluconazole as part of a comprehensive therapeutic approach to address various infections during the hospital stay. The patient, unfortunately, succumbed at three months of age due to cardiac arrest secondary to hypocalcaemia and an underlying heart abnormality exacerbated by recurrent infections.

Premature death is noted in 4% of 22q11.2 DiGeorge syndrome newborns, often attributed to cardiac problems, hypocalcaemia, and airway malacia, typically occurring between 3 and 4 months of age [6]. Antibiotic prophylaxis may improve outcomes in moderately phenotypic DiGeorge syndrome patients by reducing the risk of infections.

Conclusion

Early identification and the implementation of a well-coordinated care plan can significantly enhance the quality of life for individuals affected by this rare illness. The presented case

underscores the critical importance of conducting thorough and comprehensive ultrasound examinations during the early stages of pregnancy. These examinations play a vital role in assessing the necessity for specific genetic tests, including FISH analysis, in conjunction with routine cytogenetic tests, facilitating an early and accurate prenatal diagnosis.

Moreover, it is imperative that couples are provided with the option of prenatal genetic counselling for any future pregnancies. This counselling serves as a valuable resource in helping them make informed decisions regarding the management of potential genetic conditions, fostering a proactive and supportive approach to reproductive health.

Conflicts of interest

The authors declare no conflicts of interest.

References

[1]. Rebecca H, Sullivan B, Kathleen E. Nelson Textbook of Pediatrics. In: Kleigman R, St Geme J, Blum N, Shah S, Tasker R, Wilson K, editors. Nelson Textbook of Pediatrics. 21st ed. Elsevier India Private Limited; 2018. p. 1112–3.

[2]. Bernstein D. Nelson Textbook of Pediatrics. In: Kleigman R, St Geme J, Blum N, Shah S, Tasker R, Wilson K, editors. Nelson Textbook of Pediatrics. 21st ed. Elsevier India Private Limited; 2018. p. 2367–8.

[3]. Jones KL, Jones MC, Del Campo M. Smith's Recognizable Patterns of Human Malformation, Eighth Edition. 8th ed. Elsevier;

[4]. Arachichi K, Devasiri I, Rathuwtihana C, Wackwella W, Atapattu N. DiGeorge syndrome: A case report. Journal of the Ruhunu Clinical Society. 2015;(2):22–3.

[5]. Akçakuş M, Güneş T, Kurtoğlu S, Çetin N, Özkul Y, Narin N, et al. Asymmetric crying facies associated with congenital hypoparathyroidism and 22q11 deletion. Turkish Journal of Pediatrics. 2004;46(2):191–3.

[6]. Repetto GM, Guzmán ML, Delgado I, Loyola H, Palomares M, Lay-Son G, et al. Case fatality rate and associated factors in patients with 22q11 microdeletion syndrome: A retrospective cohort study. BMJ Open. 2014;4(11):1–5.

[7]. Balci S, Altugan FS, Alehan D, Aypar E, Baltaci V. A prenatally sonographically diagnosed conotruncal anomaly with mosaic type trisomy 21 and 22q11.2 microdeletion/diGeorge syndrome. Genetic Counseling. 2009;20(4):373–7.