

Acute Idiopathic Severe Thrombocytopaenia in a Young Child with Unidentified DiGeorge Syndrome

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ABSTRACT

Children with 22q11.2 deletion syndrome (22q11DS), also known as DiGeorge syndrome (DGS), experience an array of symptoms, including heart, skeletal, and immune system problems and developmental delays. 22q11DS is a common genetic disease characterised by broad phenotypic variability. Few studies have described haematological alterations in individuals with 22q11DS, and these abnormalities may be more frequent than previously thought. We present a case of a 3-year girl who was diagnosed with congenital heart disease during the neonatal period. At the age of 3 years, she arrived at the emergency department with a sudden history of bleeding from her nose and gums. It was discovered that she had severe thrombocytopaenia, and she was treated successfully with intravenous immunoglobulins. A genetic study revealed that the patient had DGS.

Key Words: *Chromosome 22q11.2 deletion syndrome, Congenital heart disease, Thrombocytopaenia, DiGeorge syndrome.*

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INTRODUCTION

DiGeorge syndrome (DGS) is usually detected in early life but due to different presentations may remain an undetectable disease.¹ Diagnostic methods were undiscovered before 1981, therefore people aged >45 years were undiagnosed.² This condition was first described in 1968 with a triad of immune deficiency, truncoconal cardiac defects, and hypocalcaemia. DGS is of two types; the first is partial: T-cells can be low or normal leading to incomplete T-cell immunodeficiency, and the second is complete DGS, which has no T-cells leading to complete T-cell immunodeficiency. There are very few studies discussing haematological problems in DGS.³ We aim to discuss a case of DGS with thrombocytopaenia and to review the literature.

CASE REPORT

A 3-year girl with a previously treated congenital heart issue (CHD) presented to the emergency department (ED) with sudden onset of nasal and oral bleeding.

The patient was born at term (37 + 2 weeks) to a 30-year mother (gravida 3, para 2 + 0). The antenatal scans were normal, and the parents were non-consanguineous. APGAR scores were 8, 9, and 9 at 1, 5, and 10 minutes, respectively.

Birth weight was 2.32 kg (below 3rd percentile), height was 46 cm (5th percentile), and head circumference was 34 cm (54th percentile). At the age of 12 hours, in the postpartum ward, oxygen desaturation was observed reaching 80% without respiratory distress, and a systolic murmur was heard over the pericardium. The patient was admitted to the neonatal intensive care unit (NICU) due to suspicion of congenital heart disease (CHD). Chest x-ray revealed abnormal cardiac shadow. Urgent echocardiogram showed situs solitus, levo cordia, atrioventricular normal concordance, normal ventricular function and ejection fraction, hypertrophied right ventricle with thick wall, small atrial septal defect with left-to-right shunt, ventricular septal defect measuring 7 mm with biventricular shunt, aorta overriding the interventricular septum by 50%, mild tricuspid regurgitation, and no mitral regurgitation. The final diagnosis was tetralogy of Fallot. Laboratory tests done in the NICU are shown in Table I.

She stayed in the NICU for two months due to her inability to wean from oxygen. She was transferred to a higher cardiac centre (Prince Sultan Cardiac Centre), and was operated on successfully at the age of two months without any complications. She was discharged home in good condition without long-term medications, with follow-ups with cardiology in the tertiary centre. Echocardiography post-surgery showed situs solitus, levocardia, atrioventricular / ventriculoarterial concordance, intact internal septum, mild tricuspid regurgitation, no mitral regurgitation, dilated right ventricle with good function, no ventricular septal defect, no aortic insufficiency, confluent branch of pulmonary artery, patent aortic arch, and no patent ductus arteriosus.

She was presented to the ED with a history of sudden oral and nasal bleeding, multiple ecchymoses with petechial rash, but no fever. There was no blood in urine or stool. No bleeding from other sites.

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Table I: Laboratory results of tests done in the NICU.

Lab tests	Lab results	Normal ranges
TSH	5.2 Uiu/ml	0.5-5 Uiu/ml
WBC	$13.2 \times 10^9/L$	$4-11 \times 10^9/L$
Haemoglobin	15.8 g/dl	12-16 gram/dl
Platelets	$202 \times 10^9/L$	$140-440 \times 10^9/L$
Calcium	1.94 mmol/l	2.23-2.58 mmol/L
Albumin	32 g/L	35-50 g/L
Magnesium	0.80 mmol/L	0.74-1.03 mmol/L
Phosphorus	1.63 mmol/L	0.78-1.53 mmol/L
Alkaline phosphatase	222 U/L	32-91 U/L
Corrected calcium	2.11 mmol/L	2.2-2.7 mmol/L
Sodium	137 mmol/l	136-144 mmol/L
Potassium	4.8 mmol/L	3.6-5.1 mmol/L
Chloride	104 mmol/L	101-111 mmol/L
Urea	4.5 mmol/L	2.9-9.3 mmol/L
Creatinine	79.2 umol/L	27-88 umol/L
Total protein	60 g/L	61-80 g/L
Total bilirubin	53.8 µmol/L	<34.2 µmol/L
Direct bilirubin	3.8 µmol/L	1.7-8.6 µmol/L
Alanine aminotransferase	9 U/L	8-29 U/L
AST	42 U/L	14-37 U/L
GGT	111 U/L	8-23 U/L
Reticulocytes, %	2.3 %	0.5-2.5 %

TSH, Thyroid stimulating hormone; WBC, White blood cells; AST, Aspartate aminotransferase; GGT, Gamma glutamyl transferase.

Table II: Test results on admission in the emergency room.

Lab tests	Lab results	Normal ranges
WBC	$8.2 \times 10^9/L$	$4-11 \times 10^9/L$
Calcium	2.21 mmol/l	2.23-2.58 mmol/L
Albumin	41 g/L	35-50 g/L
Magnesium	0.81 mmol/L	0.74-1.03 mmol/L
Phosphorus	1.76 mmol/L	0.78-1.53 mmol/L
Alkaline phosphatase	198 U/L	32-91 U/L
Corrected calcium	2.20 mmol/L	2.2-2.7 mmol/L
Sodium	136 mmol/l	136-144 mmol/L
Potassium	4.4 mmol/L	3.6-5.1 mmol/L
Chloride	107 mmol/L	101-111 mmol/L
Urea	6.6 mmol/L	2.9-9.3 mmol/L
Creatinine	24 umol/L	27-88 umol/L
Total protein	73 g/L	61-80 g/L
Total bilirubin	10.5 umol/L	<34.2 umol/L
Direct bilirubin	2.5 umol/L	1.7-8.6 umol/L
Alanine aminotransferase	9 U/L	8-29 U/L
AST	12 U/L	14-37 U/L
GGT	7 U/L	8-23 U/L
Reticulocytes, %	2.15 %	0.5-2.5 %
TSH	2.12 Uiu/ml	0.79-5.85 Uiu/ml
Free T4	12.94 pmol/L	9.52-5.18 pmol/L
Vitamin D (25-hydroxy)	18.20 ng/ml	17.37-48.48 ng/ml
Lactose dehydrogenase	528 U/L	142-297 U/L

TSH, Thyroid stimulating hormone; WBC, White blood cells; AST, Aspartate aminotransferase; GGT, Gamma glutamyl transferase.

On systemic examination, she was ill, temperature was 37.1°C, heart rate 132 beats/minute, blood pressure 98/62 mmHg, and respiratory rate was 28 breaths/minutes. Central nervous system examination revealed Glasgow coma scale of 15/15, pupils were reactive bilaterally, and there was normal limb power, tone, and reflexes. Cardiovascular system examination revealed regular pulse with good volume, capillary refill time less than two seconds, surgical scar, no audible murmur, and no added sounds. Chest examination showed equal air entry bilaterally. Oxygen saturation was 96% on room air. A gastroenterology examination revealed soft abdomen, and no tender liver or organomegaly.

In the emergency room, the initial laboratory results revealed haemoglobin of 8 g/dl, and platelets $3 \times 10^9/L$.

Peripheral blood smear showed severe thrombocytopenia, anaemia, and mild leucocytosis. Red blood cells (RBCs) were hypochromic and microcytic, with anisopoikilocytosis +2, occasional poly-chromasia, and few fragmented RBCs. White blood cells showed adequate neutrophils with mild left-shifted maturation, occasional toxic granulation, and occasional activated lymphocytes. No classical blasts were noted. Platelets were normal sized, with no platelet clumps. The rest of the laboratory results are shown in Table II.

She was admitted and received intravenous immune globulin twice and tranexamic acid. She was diagnosed initially with idiopathic thrombocytopenic purpura (ITP) with the expectation of improvement as immune globulins can

increase platelet count. The bleeding stopped, and her platelets rose to $65 \times 10^9/L$. Her condition improved. Whole exome sequencing (WES) was sent as advised by the haematologist as the child had unexplained low platelets. The result was obtained after several months and was consistent with the genetic diagnosis of autosomal dominant 22q11DS. The patient has regular follow-ups with the haematology team for signs and symptoms of bleeding and regular monitoring of complete blood count for thrombocytopenia.

DISCUSSION

A 3-year girl with surgical repair of tetralogy of Fallot at the age of two months presented with thrombocytopenia and was subsequently diagnosed with DGS.

The DGS is a rare congenital disorder characterised by broad phenotypic variability. Macro-thrombocytopenia has been frequently observed in patients with DGS, which is characterised by a significant drop in platelet count with a concurrent increase in the size and volume of the platelets. However, this is not accompanied by an increased risk of bleeding. Macro-thrombocytopenia in DGS patients is due to heterozygosity for a deletion of the *GPIb* gene. Macro-thrombocytopenia appears to be the most common cause of thrombocytopenia in patients with DGS. Some studies indicate that it may also be used as a potential clinical marker of the disease.⁴

Overall, children with DGS do not have a high risk of bleeding. Some studies showed that thrombocytopenia and macro-thrombocytopenia of more than $10/fL$ could be utilised as valid indicators for diagnosis of DGS.

Patients with macro-thrombocytopenia in comparison with patients who have DGS have less severe bleeding tendency.⁵ In most patients with ITP the symptoms resolve spontaneously, but some patients have different bleeding times, phenotypes and responses to applied treatment, particularly in patients with chronic ITP, multi-lineage cytopenias or others where treatment is more complicated.⁶ As mentioned in this case, the patient showed good response to intravenous immunoglobulins as platelets raised from $3 \times 10^9/L$ to $65 \times 10^9/L$ and the bleeding stopped.⁷ Our case underwent a major cardiac surgery at the age of 2 months which was completed successfully without complications or bleeding tendency. Avoiding excessive blood transfusion is crucial to avoid worsening bleeding postoperatively.⁸

It should also be noted that DiGeorge patients are prone to post-cardiac surgeries to prolonged intubation, the length of stay in intensive care units, ventilator-associated infection, urinary tract infection, and bacteremia, which can lead to

sepsis and worsening thrombocytopenia more than other CHDs post-cardiac surgeries.⁹ Patients with cyanotic CHDs are often discovered to have haematological derangements, and while haemoglobin levels are usually seen to rise, significant thrombocytopenia is found in these patients. The low platelet counts often pose a risk peri-surgically and can also affect the surgical outcomes of the patient.¹⁰

In conclusion, for dysmorphic patients with thrombocytopenia for unknown reasons, genetic study should be considered. Not all thrombocytopenia in DGS patients is macro-thrombocytopenic. Critical congenital heart defects that need surgery should be done as soon as possible as they can affect life expectancy. Vaccinations should be monitored and given correctly due to immune-deficiency of these patients. Bleeding can present lately as in this patient. Finally, DGS requires multidisciplinary team workup for its proper management.

PATIENT'S CONSENT:

Consent was obtained from the patient's parents.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

BGA, AS, AS: Managing the patient.

IY: Collecting data.

MM: General paediatric admitted under him.

All authors approved the final version of the manuscript to be published.

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