Severe congenital neutropenia due to G6PC3 deficiency: Case series of five patients and literature review

Natalia Velez-Tirado | Marco Antonio Yamazaki-Nakashimada | Enrique Lopez Valentín | Armando Partida-Gaytan | Selma C. Scheffler-Mendoza | Genny M. Chaia Semerena | Aristóteles Alvarez-Cardona | Marcos Alejandro Suárez Gutiérrez | Edgar Alejandro Medina Torres | Patricia Baeza Capetillo | Tatjana Hirschmugl | Wojciech Garncarz | Sara Elva Espinosa-Padilla | Jesús Aguirre Hernández | Christoph Klein | Kaan Boztug | Saul O. Lugo Reyes

1Clinical Immunology, Clinica del Country, Bogotá, Colombia  
2Clinical Immunology Service at the National Institute of Pediatrics, Mexico City, Mexico  
3Allergy Department, Hospital del Niño de Toluca, Toluca, Mexico  
4Fundacion Mexicana Para Niños Con Immunodeficiencias, AC, Mexico City, Mexico  
5Hospital Angeles Metropolitan, Mexico City, Mexico  
6Unidad de Investigacion en Inmunologia Clinica y Alergia Aguascalientes, Aguascalientes, Mexico  
7Immune Deficiencies Lab at the National Institute of Pediatrics, Mexico City, Mexico  
8Genetics Department, Hospital Infantil de Mexico ‘Federico Gómez’, Mexico City, Mexico  
9Laboratory of Genomics, Genetics and Bioinformatics, Hospital Infantil de Mexico ‘Federico Gómez’, Mexico City, Mexico  
10CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria  
11Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, Vienna, Austria  
12St. Anna Children’s Cancer Research Institute (CCRI), Vienna, Austria  
13Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Austria  
14Department of Pediatrics and Adolescent Medicine, St. Anna Children’s Hospital, Medical University of Vienna, Vienna, Austria  
15Department of Pediatrics, Dr. von Hauner Children’s Hospital, University Hospital, LMU Munich, Munich, Germany

Abstract

Background and objectives: Glucose-6-phosphate catalytic subunit 3 (G6PC3) deficiency is characterized by severe congenital neutropenia with recurrent pyogenic infections, a prominent superficial venous pattern and cardiovascular and urogenital malformations caused by an alteration of glucose homeostasis, with increased endoplasmic reticulum stress and cell apoptosis.

Methods: We reviewed our patients with G6PC3 deficiency diagnosed along the last decade in Mexico; we also searched the PubMed/Medline database for the terms (‘G6PC3 deficiency’ OR ‘Dursun syndrome’ OR ‘Severe congenital neutropenia type 4’), and selected articles published in English from 2009 to 2020.
INTRODUCTION

While rare diseases are individually infrequent, collectively they afflict around 10% of the world population. Patients with rare diseases typically must endure a ‘diagnostic odyssey’ that may take several years before receiving a correct diagnosis and treatment. Inborn errors of immunity (IEI) are a group of rare congenital diseases caused by monogenic germline variants that result in the modification of protein expression or function, affecting the development, function and homeostasis of the immune system.1 IEI comprise a wide spectrum of disorders that may manifest not only with increased susceptibility to infections but also with inflammation, autoimmunity, allergy or malignancy.

In 1950, Rolf Kostmann first described ‘hereditary agranulocytosis’, or severe congenital neutropenia (SCN), characterized by an early onset of recurrent bacterial and fungal infections of the mouth, umbilical stump, skin, gastrointestinal tract, bones, lungs and lymph nodes.2 Although pathogenic variants in ELANE are the most common genetic aetiology of autosomal dominant (AD) SCN, several others have been described in the last 2 decades: X-linked WAS gain of function (GOF); autosomal recessive (AR) HAX1, GFI1, CSF3R and G6PC3 loss of function (LOF) and AD TCIRG1 haploinsufficiency. The molecular cause is unknown in about 30% of patients with SCN.

In 2009, Boztug and Klein reported3 a series of 12 patients with congenital neutropenia and various cardiovascular and urogenital developmental anomalies, who had homozygous and compound heterozygous variants in the gene-encoding glucose-6-phosphatase catalytic subunit 3 (G6PC3 deficiency, also known as type 4 SCN, OMIM #612541), as well as prominent superficial veins (mainly in trunk and limbs). G6PC3 is located on chromosome 17q21 and spans 6 exons.

Independently, a pair of Turkish siblings were reported with pulmonary arterial hypertension, and other abnormalities including cardiac, haematological and skeletal defects.4 Over the last decade, the spectrum of the disease has continuously widened to include non-syndromic forms and new features.5 Here, we describe 5 patients from Mexico, and review the available literature for clinical features, genetic variants, treatment and outcome of 89 more patients with G6PC3 deficiency.

CASE REPORTS

Patient 1

A 3-month-old male, born to non-consanguineous parents from rural central Mexico, was born prematurely at 35 weeks and admitted to the neonatal intensive care unit for extensive oedema and ecchymoses, with respiratory distress that required mechanical ventilation. He was started on intravenous antibiotics for pneumonia and sepsis.

Physical examination found low weight, a low-grade systolic murmur, hepatomegaly and cryptorchidism; prominent superficial veins in thorax, abdomen and all 4 limbs were later noted. Laboratory workup reported transient-variable anaemia, lymphopaenia and thrombocytopenia; as well as severe persistent neutropenia and pan-hypogammaglobulinemia. An echocardiogram showed a persistent foramen ovale (4 mm) with bidirectional shunt and pulmonary arterial hypertension at 58 mm Hg. Abdominal ultrasound revealed pyloric stenosis and severe bilateral hydronephrosis.

Filgrastim (granulocyte colony-stimulating factor, G-CSF) was started at 3-5 µg/kg/d, with a spectacular but transient increase in neutrophil count, as well as prophylactic antibiotics (trimethoprim/sulfamethoxazole and itraconazole) and monthly intravenous immunoglobulin.

Results: We found 89 patients reported from at least 14 countries in 4 continents. We describe five new cases from Mexico. Of the 94 patients, 56% are male, 48% from Middle East countries and none of them had adverse reactions to live vaccines; all presented with at least 1 severe infection prior to age 2. Seventy-five percent had syndromic features, mainly atrial septal defect in 55% and prominent superficial veins in 62%.

Conclusions: With a total of 94 patients reported in the past decade, we delineate the most frequent laboratory and genetic features, their treatment and outcomes, and to expand the knowledge of syndromic and non-syndromic phenotypes in these patients.
An homozygous single-nucleotide deletion in exon 1 of G6PC3 (c.210delC, p. Phe71SerfsTer46) was identified through Sanger sequencing, a variant previously reported. In time, the dosage of filgrastim had to be increased up to 22 mg/kg/d to achieve an acceptable neutrophil count. Due to this severe and early presentation, haematopoietic stem cell transplantation (HSCT) was performed in this patient at the age of 15 months. Unfortunately, he developed neutropenic colitis and died of sepsis on day +29.

2.2 | Patient 2

A 15-year-old female, born to non-consanguineous parents from a small rural community (300 inhabitants), was admitted for a 6-year history of episodic diarrhoea and intense generalized abdominal pain, each episode lasting between 7 and 14 days, for which she had received multiple antibiotic treatments with slight improvement. Her past medical history also included pneumonia at 4 months old, as well as recurrent otitis media and other upper airway infections.

On admission, we found a severely undernourished patient, with prominent superficial veins, finger clubbing, brachymetatarsia of the third toes and bilateral sensorineural hearing loss. Laboratory workup revealed anaemia, intermittent neutropenia and lymphopaenia. Colonoscopy and histopathology were compatible with Crohn’s disease; echocardiography revealed mild tricuspid insufficiency.

She started treatment with mesalazine, trimethoprim-sulfamethoxazole (TMP-SMZ), prednisone, IVIG every 21 days and filgrastim (G-CSF, 10 mcg/kg/d). Through Sanger sequencing, a homozygous single-nucleotide deletion was found in exon 1 of G6PC3 (c.210delC, p. Phe71SerfsTer46), the same variant identified in Patient 1.

At age 16, she developed bronchopulmonary aspergillosis and was treated with voriconazole. Despite good adherence, complete remission of IBD was never achieved. At 17 years, she presented with acute abdominal pain, fever and vomit; she died with abdominal sepsis after intestinal perforation. Remarkably, prior to this catastrophic event, she had been asymptomatic. The autopsy revealed severe extensive bowel inflammation, which was at odds with her clinical symptoms and signs.

2.3 | Patient 3

A 3-month-old female patient, born to non-consanguineous Mexican parents, with a family history of 3 paternal uncles who died before the age of 5 years. She first presented with neonatal sepsis requiring intravenous antibiotics, after which she had 5 episodes of pneumonia and a surgically corrected rectovaginal fistula.

On physical examination, we found severe chronic malnutrition, prominent superficial veins in her abdominal wall, bilateral sensorineural hearing loss and supplemental oxygen dependence. Her clinical assessment revealed severe neutropenia, atrial septal defect and severe pulmonary damage due to multiple atelectasia and bronchiectasis, associated with pulmonary arterial hypertension. Whole-exome sequencing identified the same homozygous single-nucleotide deletion in G6PC3 (c.210delC; p. Phe71SerfsTer46) as in patients 1 through 4. Patient 3 is currently 3 years old, alive and well, under treatment with granulocyte colony-stimulating factor (G-CSF, filgrastim–30 mcg/kg/d).

2.4 | Patient 4

A 9-year-old boy from northern Mexico, with no known consanguinity or family history of infections or early deaths. He started at age 3 months with suppurative otitis media and pneumonia that required admission to the intensive care unit (ICU) and was hospitalized for a month. Neutropenia was recorded since then, with absolute neutrophil counts (ANC) within the range 450–790/mm³, which responded well to filgrastim (G-CSF).

However, despite the increase in neutrophil numbers, the patient persisted with multiple respiratory tract infections requiring frequent hospitalizations and parenteral antibiotics up to 5 years of age. He also presented with oral, finger and perianal abscesses, without any isolates. From 6 years on, the frequency of infections decreased to 1–2 per year. On physical examination, weight and height were normal; he had a prominent superficial venous pattern in trunk and limbs, as well as redundant skin folds in the neck and a left inguinal hernia.

Laboratory workup reported intermittent thrombocytopenia and persistent lymphopaenia; bone marrow aspiration showed myeloid cell hypoplasia and non-specific findings. An echocardiogram revealed persistent foramen ovale (corrected percutaneously with an Amplatzer device), and pulmonary hypertension of 45mm/Hg, whereas a Doppler ultrasound of the liver documented compensated portal hypertension. Percutaneous liver biopsy reported sinusoid fibrosis and steatosis.

Sanger sequencing identified a compound heterozygous genotype, with variants in exons 1 and 4 of G6PC3: the same single-nucleotide deletion (c.210delC, p. Phe71SerfsTer46) and a nonsense transition (c.481C>T, p. Arg161*) respectively. The patient is currently alive and well, under treatment with G-CSF 5 mcg/kg/day.
2.5 Patient 5

A 2-year-old female, born to non-consanguineous Mexican parents, was referred to our care for a history of cow’s milk allergy, allergic asthma and rhinitis, recurrent otitis media, sepsis, urinary tract infection, autoimmune colitis and disseminated herpes zoster.

On physical examination, she did not have any syndromic features. Complete blood count reported severe neutropenia, anaemia, intermittent lymphopaenia and thrombocytopenia. Through whole-exome sequencing analysis, a compound heterozygous genotype consisting of 2 single-nucleotide deletions in exons 1 and 4 of G6PC3 was identified (c.210delC, p. Ile70HisfsTer46; c.421del, p. Trp141GlyfsTer2); this second frameshift variant has not been previously described and is not found in gnomAD. The patient is alive under treatment with G-CSF 3 mcg/kg/day and prophylaxis with TMP-SMZ and fluconazole.

2.6 Ethics approval

This case series study was granted exemption by the National Institute of Pediatrics Research and Ethics Committee due to its retrospective design. All authors subscribe the 1964 Declaration of Helsinki by the World Medical Organization and its later amendments regarding human experimentation. All patients or their guardians consented to genetic diagnostic research and publication.

2.7 Review of the literature

We searched the PubMed/Medline database for the terms ('G6PC3 deficiency' OR 'Dursun syndrome' OR 'Severe congenital neutropenia type 4'), and selected articles published in English from 2009 to 2020. We found 89 patients reported from at least 14 countries in 4 continents (See Tables 1-3. Not all reports included the country of origin). Table 1 describes their origins, demographic, clinical and laboratory features, treatment and outcome. Table 2 collects their genetic variants. In Table 3, we summarize the most common features and findings.

Ninety-four patients were included in this review (whenever the denominator is less than 94, that attribute was not available for some patients). The distribution of the disease was similar between males (52/92, 56%) and females. Most cases were from Middle East countries (47.8%). None of the patients had adverse reactions to live vaccines such as BCG. All patients presented at least 1 severe infection prior to 2 years of age; however, only 28.5% (26/91) were diagnosed before the age of 2.

Syndromic features were identified in 71/94 (75.5%) of the patients. The most frequent alterations were cardiovascular defects, mainly atrial septal defect in 52/94 (55.3%), valve disease 21/94 (22.3%), patent ductus arteriosus 10/94 (10.6%) and prominent superficial veins 58/94 (61.7%). Some of the cardiovascular malformations resulted in pulmonary hypertension secondary to pulmonary overflow. However, a group of patients had primary pulmonary hypertension not related to congenital cardiopathy. Thirty-seven patients (39.3%) presented with urological or genital malformations, which were more commonly seen in male patients, being cryptorchidism the most prevalent among those: 21/52 (40.53%). Other reported anomalies were urachal fistula, unilateral or bilateral inguinal hernia, hydronephrosis, genital microsia and micropenis. Endocrine abnormalities were described in 28/94 patients (30%), with variable manifestations ranging from growth retardation in 12/94 (12.7%) to puberal delay (in 6/94, 6.3%), and growth hormone deficiency (4/94, 4.3%; Figures 1 and 2).

Other non-haematological features were sensorineural hearing loss in 12/94 (12.7%), developmental delay (11/94, 12%) and microcephaly (5/94, 5.3%). Inflammatory bowel disease was present in 10/94 (10.6%) of patients, with a higher prevalence in the syndromic group (70%); 2 of these patients also had oculocutaneous albinism, 3 had persistent lymphopaenia and 1 T cell lymphopaenia, suggesting a more severe compromise. Splenomegaly was reported in 6/94 (6.3%).

Immunological analysis was not performed homogeneously in all patients; flow cytometry, immunoglobulins or lymphoproliferation was available only for 21/94. Although they all had severe neutropenia, some showed an intermittent increase in neutrophil counts. Intermittent thrombocytopenia was reported in 37/94 patients (39.3%), and 17 of 94 (18%) had lymphocyte counts below 1500/mcL. Nineteen patients had their serum immunoglobulin levels measured, of which 9 (47.3%) presented with hypergammaglobulinaemia and 2 hypogammaglobulinaemia (10.5%).

Treatment was described in 76 patients; 1 patient did not require any pharmacological intervention, while 63/76 (82.8%) were given G-CSF, 2.6% received pegfilgrastim and 3.9% received prophylactic co-trimoxazole as only treatment; IVIG was administered in 5/76 (6.5%) patients. Only 3 patients (4%) received haematopoietic stem cell transplant (HSCT). Patient 69 underwent HSCT due to severe IBD refractory to medical treatment and showed complete resolution of gastrointestinal symptoms; whereas patient 70 was transplanted because of the severe presentation of the disease and died from complications associated with the procedure. Long-term
| Author, Year | Individual | Country | Age (years) | Sex | Clinical remarks | Cytopenias | Immunoglobulins | Bone marrow | Treatment | Outcome |
|-------------|------------|---------|-------------|-----|------------------|------------|-----------------|-------------|-----------|---------|
| Boztug, 2009 | P1         | Turkish | 6           | M   | ASD              | ANC 60-246/μL | NA              | Maturation arrest at the stage of promyelocytes/myelocytes | G-CSF | Alive   |
|             |            |         |             |     | Cryptorchidism   | Intermittent thrombocytopenia |                | Cardiac surgery |         |         |
|             |            |         |             |     | Increased venous marking | Hepatoesplenomegaly |                |             |           |         |
|             |            |         |             |     | Mitral insufficiency | ANC 54-240/μL | NA              | Maturation arrest at the stage of promyelocytes/myelocytes | G-CSF | Alive   |
|             |            |         |             |     | Increased venous marking | Hepatoesplenomegaly |                | Cardiac surgery |         |         |
|             |            |         |             |     | Increased venous marking | ANC 0-61/μL | NA              | Maturation arrest at the stage of promyelocytes/myelocytes | G-CSF | Alive   |
|             |            |         |             |     | Mitral insufficiency | ANC 0-322/μL | NA              | Cardiac surgery |         |         |
|             |            |         |             |     | Increased venous marking | ANC 0-25-84/μL | NA              | Maturation arrest at the stage of promyelocytes/myelocytes | G-CSF | Alive   |
|             |            |         |             |     | Mitral insufficiency | ANC 0-3.000/μL | NA              | Cardiac surgery |         |         |
|             |            |         |             |     | Increased venous marking | ANC 200-500/μL | NA              | Cardiac surgery |         |         |
|             |            |         |             |     | Urachal fistula | ANC 175-210/μL | NA              | Cardiac surgery |         |         |
|             |            |         |             |     | Increased venous marking | ANC 200-500/μL | NA              | Cardiac surgery |         |         |
|             |            |         |             |     | Myopathy | ANC 200-500/μL | NA              | Cardiac surgery |         |         |
|             |            |         |             |     | Increased venous marking | ANC 200-500/μL | NA              | Cardiac surgery |         |         |
|             |            |         |             |     | Increased venous marking | ANC 200-500/μL | NA              | Cardiac surgery |         |         |

(Continues)
| Author          | Individual | Country     | Age (years)<sup>a</sup> | Sex<sup>b</sup> | Clinical remarks                                      | Cytopenias         | Immunoglobulins | Bone marrow  | Treatment     | Outcome     |
|-----------------|------------|-------------|--------------------------|----------------|-------------------------------------------------------|--------------------|-----------------|--------------|--------------|-------------|
| Boztug, 2009    | P11        | Persian     | 11                       | M             | ASD PDA                                               | ANC 250-440/μL     | NA              | NA           | G-CSF        | Alive       |
| Boztug, 2009    | P12        | Lebanese    | 12                       | M             | Cryptorchidism Bilateral inguinal hernia Cleft palate | ANC 615-2000/μL    | NA              | NA           | G-CSF        | Alive       |
| Eghballi, 2009  | P13        | Iran        | 0                        | M             | Hydronephrosis of the left kidney ASD and PDA        | ANC 234/μL         | IgG 672 mg/dL (350-1180) | NA          | Maturation arrest in myeloid series | G-CSF        | Alive       |
| Dursun, 2009    | P14        | Turkish     | 0.3                      | F             | ASD Mild PH Hypertelorism Pectus carinatum Hypoplastic thymus | ANC 300-630/μL ALC 336-3800/μL Platelets 141.000 - 222.000/μL Hb 6.5 g/dL | NA              | Hypocellularity with normal distribution of all series | NA          | Deceased     |
| Durson, 2009    | P15        | Turkish     | 0.2                      | M             | ASD Mild PH Pectus carinatum Cryptorchidism Hypoplastic thymus | ANC 112-6000/μL ALC 154-3680/μL Platelets 35.000-446.000/μL Hb 7.8 g/dL | NA              | Dysplastic changes in all lineages, megaloblastic changes in myeloid and erythroid cell lines and severe vacuolization in myeloid series | G-CSF 10 mcg/kg/day | Deceased     |
| Arostegui, 2009 | P16        | Moroccan    | 22                       | M             | ASD Bilateral cryptorchidism Prominent subcutaneous venous circulation Poor growth | ANC 50-540/μL Hb 9.5 g/dL | NA              | Paucity of granulocyte series beyond the promyelocyte stage | rhG-CSF 7.5 mcg/kg every 48h | NA          |
| Xia, 2009       | P17        | USA         | NA                       | NA            | ASD                                                   | Neutropenia        | NA              | NA           | NA           | NA          |
| Xia, 2009       | P18        | USA         | NA                       | NA            | ASD Coronary aneurysm                                  | Intermittent thrombocytopenia | NA              | NA           | NA           | NA          |
| Author         | Individual | Country  | Age (years)
|----------------|------------|----------|-------------------|
| McDermott, 2010 | P19        | USA      | 13                |
|                |            | (Caucasian) |                |
|                |            |          | M                |
|                |            |          | 9                |
|                |            |          | M                |
| Germeshausen, 2010 | P21     | Turkish  | 24                |
|                |            |          | F                |
| Germeshausen, 2010 | P22     | Caucasian| 20                |
|                |            |          | M                |
| Germeshausen, 2010 | P23     | Caucasian| 5                 |
|                |            |          | M                |
| Hayee, 2011    | P24        | Pakistan | 20                |
|                |            |          | M                |
| Hayee, 2011    | P25        | Pakistan | 28                |
|                |            |          | M                |

**Clinical remarks**

- Permeable foramen ovale
- Mild PHT
- Cryptorchidism
- Prominent superficial veins
- Sensorineural hearing loss
- Heart valve abnormalities
- Poor growth
- Microcephaly
- Ligamentous laxity
- Bronchiectasis
- ASD
- Prominent superficial veins
- Poor growth
- Microcephaly
- Sensorineural hearing loss
- Bronchiectasis
- Hypogonadotropic hypogonadism
- ASD
- Mild mitral and tricuspid insufficiency
- Prominent superficial venous pattern
- Learning difficulties
- Cryptorchidism
- Genital dysplasia
- Microcephaly
- ASD
- Prominent superficial venous pattern
- Neurodevelopmental abnormalities
- Recurrent oral ulceration
- Neurodevelopmental abnormalities
- ASD
- Granulomatous IBD
- Splenomegaly
- Digital cubbing
- Short stature

**Bone marrow**

- Full myeloid maturation
- Increased expression of CXCR4
- Normocellular with mild left-sided shift

**Immunoglobulins**

- NA
- NA
- NA
- NA
- NA

**Cytopenias**

- ANC 50-900/μL
- ANC 50-900/μL
- ANC 200-700/μL
- ANC 0-30/μL
- ANC 300-350/μL
- NA
- NA
- NA

**Treatment**

- G-CSF 5 mcg/kg/day
- G-CSF 5 mcg/kg/day
- NA
- NA
- NA

**Outcome**

- Alive
- Alive
- Alive
- NA
- NA

(Continues)
| Author | Individual | Age (Years) | Country | Sex | Clinical Remarks | Bone marrow | Treatment | Outcome |
|--------|------------|-------------|---------|-----|------------------|-------------|-----------|---------|
| Gatti, 2011 | P26 | 10 | Ecuador | M | ASD | Prominent superficial veins and varicose veins | NA | G-CSF 1.7 mcg/kg/day | Alive |
| Cullinane, 2011 | P27 | 32 | USA (Caucasian) | F | Oculocutaneous albinism | Prominent superficial veins and varicose veins | NA | Alive |
| Banka, 2011 | P28 | 29 | Israel | F | Small for gestation at birth | Prominent superficial veins and varicose veins | NA | Alive |
| Banka, 2011 | P29 | 26 | Israel | M | ASD | Mild learning disability | NA | Alive |
| Banka, 2011 | P30 | 25 | Israel | F | ASD | Mild learning disability | NA | Deceased |

**TABLE 1** (Continued)
| Author       | Individual | Country | Age (years) | Sex | Clinical remarks                        | Cytopenias               | Immunoglobulins | Bone marrow | Treatment            | Outcome |
|--------------|------------|---------|-------------|-----|-----------------------------------------|--------------------------|-----------------|-------------|----------------------|---------|
| Banka, 2011  | P31        | Israel  | 2           | M   | Pulmonary valve stenosis                | ANC 400-7,700/μL         | NA              | All stages of  | NA                   | Alive   |
|              |            |         |             |     | ASD and PDA                             | Monocytosis              |                 | myelopoiesis seen |                       |         |
|              |            |         |             |     | Cryptorchidism                          | Lymphopaenia             |                 | without any     |                       |         |
|              |            |         |             |     | Mild-to-moderate                        |                          |                 | myeloid        | G-CSF 5-10 mcg/  |         |
|              |            |         |             |     | development delay                       |                          |                 | maturation     | kg/day                |         |
|              |            |         |             |     | Prominent superficial                    |                          |                 | arrest        |                      |         |
|              |            |         |             |     | venous pattern                          |                          |                 |              |                      |         |
|              |            |         |             |     | Pectus carinatum                        |                          |                 |              |                      |         |
|              |            |         |             |     | PH                                      |                          |                 |              |                      |         |
| Alizadeh, 2011 | P32        | Persian | 0.2         | M   | ASD                                     | ANC 40-170/μL             | NA              | Maturation arrest in | G-CSF 5-10 mcg/  | Deceased |
|              |            |         |             |     | Failure to thrive                       |                          |                 | myelocyte stage | kg/day                |         |
| Alizadeh, 2011 | P33        | Persian | 4           | M   | ASD                                     | ANC 28-450/μL             | NA              | Maturation arrest in | G-CSF 3-5 mcg/  | Alive    |
|              |            |         |             |     | Unilateral hydronephrosis                |                          |                 | myelocyte stage | kg 2 times per week |         |
|              |            |         |             |     | Prominent superficial                    |                          |                 |              |                      |         |
|              |            |         |             |     | venous pattern                          |                          |                 |              |                      |         |
| Fernandez, 2012 | P34       | USA     | 20          | M   | ASD                                     | Intermittent             | NA              | NA           | G-CSF                | Deceased |
|              |            | (Caucasian) |          |     | Cryptorchidism                          | thrombocytopenia          |                 | NA           |                      |         |
|              |            |         |             |     | Oculocutaneous albinism                  | Neutropenia               |                 |              |                      |         |
|              |            |         |             |     | Mitral valve prolapse                    |                            |                 |              |                      |         |
|              |            |         |             |     | Inflammatory bowel disease               |                            |                 |              |                      |         |
|              |            |         |             |     | Hepatoesplenomegaly                      |                            |                 |              |                      |         |
|              |            |         |             |     | Intermittent                            |                            |                 |              |                      |         |
|              |            |         |             |     | thrombocytopenia                         |                            |                 |              |                      |         |
|              |            |         |             |     | Neutropenia                              |                            |                 |              |                      |         |
| Smith, 2012  | P35        | Pakistan | 9           | M   | ASD                                     | ANC 100/μL               | NA              | NA           | G-CSF                | Alive   |
|              |            |         |             |     | IBD                                     |                            |                 |              |                      |         |
|              |            |         |             |     | Splenomegaly                            |                            |                 |              |                      |         |
|              |            |         |             |     | Short stature                           |                            |                 |              |                      |         |
| Smith, 2012  | P36        | Turkey   | NA          | F   | Patent foramen ovale                    | ANC<100/μL               | NA              | NA           | G-CSF                | Alive   |
|              |            |         |             |     | Tricuspid insufficiency                  |                            |                 |              |                      |         |
| Smith, 2012  | P37        | Pakistan | 13          | M   | No abnormalities                        | ANC 400/μL               | NA              | NA           | G-CSF                | Alive   |
|              |            |         |             |     |                                          |                            |                 |              |                      |         |
| Smith, 2012  | P38        | Pakistan | 3           | M   | No abnormalities                        | ANC 450/μL               | NA              | NA           | G-CSF                | Alive   |
|              |            |         |             |     |                                          |                            |                 |              |                      |         |
| Boztug, 2012 | P39        | Arab     | 12          | F   | ASD                                     | ANC 200/μL               | NA              | NA           | G-CSF 5 mcg/kg alternate days | Alive |
|              |            |         |             |     | Small PDA                               |                            |                 |              |                      |         |
|              |            |         |             |     | Prominent superficial                    |                            |                 |              |                      |         |
|              |            |         |             |     | venous pattern                          |                            |                 |              |                      |         |
|              |            |         |             |     | Discontinuous labia majora               |                            |                 |              |                      |         |
|              |            |         |             |     | and minora                              |                            |                 |              |                      |         |
|              |            |         |             |     | Left shift                               |                            |                 |              |                      |         |
|              |            |         |             |     | myelopoiesis and reduced                 |                            |                 |              |                      |         |
|              |            |         |             |     | numbers of mature neutrophils            |                            |                 |              |                      |         |

(Continues)
| Author   | Individual | Country   | Age (years) | Sex | Clinical remarks                                      | Cytopenias                     | Immunoglobulins | Bone marrow                  | Treatment                  | Outcome |
|----------|------------|-----------|-------------|-----|------------------------------------------------------|-------------------------------|-----------------|-----------------------------|----------------------------|---------|
| Boztug, 2012 | P40       | Hispanic  | 9           | M   | ASD Prominent superficial venous pattern Frontal bossing Upturned nose Bilateral cryptorchidism Growth hormone deficiency | ANC 0-123/μL Platelets 13.000-120.000/μL | NA              | Left shift myelopoiesis and reduced numbers of mature neutrophils | G-CSF 3.3 mcg/kg 3 times per week | Alive   |
| Boztug, 2012 | P41       | Caucasian | 9           | M   | ASD Prominent superficial venous pattern Hypoplastic nipples Micropenis Erythropachydermia | ANC 100/μL | NA | Not done | G-CSF 3.7 mcg/kg 3 times per week | Alive   |
| Boztug, 2012 | P42       | Caucasian | 11          | M   | ASD PDA Bicuspid aortic valve Prominent superficial venous pattern Micropenis Cryptorchidism Erythropachydermia Mild developmental delay | ANC 276/μL Platelets 44.000-342.000/μL | NA | Left shift myelopoiesis and reduced numbers of mature neutrophils | G-CSF 5 mcg/kg 3 times per week | Alive   |
| Boztug, 2012 | P43       | Caucasian | 7           | M   | ASD Prominent superficial venous pattern Growth hormone deficiency Triangular face Left inguinal hernia | ANC 0-2.200/μL Platelets 65.000-635.000/μL | NA | Hypocellular bone marrow and left shift of granulopoiesis with few mature neutrophils | Without G-CSF supplementation | Alive   |
| Boztug, 2012 | P44       | Hispanic  | 11          | M   | ASD Mitral and tricuspid regurgitation Prominent superficial venous pattern Right cryptorchidism Bilateral inner ear hearing loss | ANC 180/μL Platelets 16.000-553.000/μL | NA | Maturation arrest at myelocyte/promyelocyte stage | NA | Alive   |
| Author        | Individual | Country    | Age (years) | Sex  | Clinical remarks                                      | Cytopenias | Immunoglobulins | Bone marrow                  | Treatment                          | Outcome   |
|---------------|------------|------------|-------------|------|-------------------------------------------------------|------------|------------------|-------------------------------|-----------------------------------|-----------|
| Boztug, 2012  | P45        | Hispanic   | 1           | M    | ASD, Prominent superficial venous pattern, Ambiguous genitalia, Hydronephrosis, Triangular face | ANC 40/μL  | NA               | Maturation arrest at myelocyte/promyelocyte stage | G-CSF 4 mcg/kg alternate days    | Alive     |
| Boztug, 2012  | P46        | Caucasian  | 16          | F    | ASD, Prominent superficial venous pattern             | ANC 300/μL | NA               | G-CSF 5 mcg once weekly        | Alive                             |           |
| Boztug, 2012  | P47        | Persian    | 11          | F    | ASD, Mild tricuspid regurgitation, Cutis laxa, Growth retardation, Triangular face | ANC 220/μL | NA               | G-CSF 5 mcg/kg once weekly     | Alive                             |           |
| Boztug, 2012  | P48        | Hispanic   | 12          | F    | Small ASD, Prominent superficial venous pattern, Growth hormone deficiency, Triangular face | ANC 480/μL | NA               | G-CSF 8 mcg/kg alternate days  | Alive                             |           |
| Boztug, 2012  | P49        | Hispanic   | 14          | M    | ASD, Prominent superficial venous pattern, Triangular face, Osteoporosis, Kawasaki disease, Growth retardation, Delayed puberty | ANC 60/μL  | NA               | G-CSF 14 mcg/kg/day            | Alive                             |           |
| Boztug, 2012  | P50        | Turkish    | 0           | M    | ASD, Prominent superficial venous pattern, Hydronephrosis, Cutis laxa, Triangular face, Frontal bossing, Micrognathia, Bilateral hearing loss, Growth retardation | ANC 4L/μL  | NA               | G-CSF 7 mcg/kg/day            | Alive                             |           |
| Author, Year | Individual | Country | Age (years) | Sex | Clinical remarks | Cytopenias | Immunoglobulins | Bone marrow | Treatment | Outcome |
|-------------|------------|---------|-------------|-----|-----------------|------------|-----------------|-------------|-----------|---------|
| Boztug, 2012 | P51        | Persian | 1           | M   | ASD             | ANC 750-900/μL | NA              | Maturation arrest at myelocyte/promyelocyte stage | G-CSF 3 mcg/kg alternate days | Alive    |
|             |            |         |             |     | Prominent superficial venous pattern |            |                 |             |           |         |
|             |            |         |             |     |                 |            |                 |             |           |         |
| Boztug, 2012 | P52        | Caucasian | 18          | M   | ASD             | ANC<100/μL | NA              | NA          | G-CSF 7.5 mcg/kg alternate days | Alive    |
|             |            |         |             |     | Bicuspid aortic valve Prominent superficial venous pattern Small kidneys Cryptorchidism Delayed puberty Growth retardation Massive splenomegaly |            |                 |             |           |         |
|             |            |         |             |     |                 |            |                 |             |           |         |
| Boztug, 2012 | P53        | Pakistani | 1           | F   | Hypoplastic left ventricle Congenital ptosis Growth retardation | ANC 200-400 | NA              | Left shift myelopoiesis and strongly reduced numbers of mature neutrophils | G-CSF 5 mcg/kg 2 times per week | Alive    |
|             |            |         |             |     |                 |            |                 |             |           |         |
|             |            |         |             |     |                 |            |                 |             |           |         |
| Boztug, 2012 | P54        | Caucasian | 7           | M   | ASD             | ANC 200/μL Platelets 97,000-332,000/μL | NA              | Left shift myelopoiesis and strongly reduced numbers of mature neutrophils | G-CSF 12 mcg/kg 3 times per week | Alive    |
|             |            |         |             |     | Prominent superficial venous pattern Cryptorchidism Right ptosis Splenomegaly |            |                 |             |           |         |
|             |            |         |             |     |                 |            |                 |             |           |         |
| Aytekin, 2013 | P55       | Turkey   | 13          | F   | Mild mitral regurgitation Frontal bossing Depressed nasal bridge Upturned nose Retromandibular Prominent superficial venous pattern on neck, chest and abdomen Poorly developed secondary sexual characteristics | Hb 9.2 g/dL ANC 200/μL | Normal              | Myelokathexis Hypercellular marrow with myeloid hyperplasia without maturation arrest | G-CSF 2.5 mcg/kg | Alive    |

*Note: ANC refers to absolute neutrophil count.*
| Author       | Individual | Country              | Age (years)* | Sex | Clinical remarks                                      | Cytopenias                                  | Immunoglobulins          | Bone marrow                      | Treatment                          | Outcome       |
|--------------|------------|----------------------|--------------|-----|-----------------------------------------------------|---------------------------------------------|---------------------------|-------------------------------|-----------------------------------|--------------|
| Banka, 2013  | P56        | Pakistan             | 10           | F   | No prominent superficial venous                     | ANC 120-1,999/μL                           | NA                        | Normocellular marrow            | G-CSF 4 mcg/kg                    | Alive        |
|              |            |                      |              |     | Normal echocardiogram                                | Platelets 131,000-201,000/μL              |                           |                               |                                   |              |
| Banka, 2013  | P57        | Pakistan             | 13           | F   | No prominent superficial venous                     | ANC 280-1080/μL                            | NA                        | Normocellular marrow            | Prophylactic Co-trimoxazole     | Alive        |
|              |            |                      |              |     | Normal echocardiogram                                |                                           |                           |                               |                                   |              |
| Banka, 2013  | P58        | Great Britain        | 8            | F   | No prominent superficial venous                     | ANC 120-570/μL                            | NA                        | Normocellular marrow            | Prophylactic Co-trimoxazole     | Alive        |
|              |            |                      |              |     | Normal echocardiogram                                | Lymphocytes 1070-1100/μL                  |                           |                               |                                   |              |
| Banka, 2013  | P59        | Great Britain        | 18           | F   | No prominent superficial venous                     | ANC 110-670/μL                            | NA                        | Normocellular marrow            | Prophylactic Co-trimoxazole     | Alive        |
|              |            |                      |              |     | Normal echocardiogram                                | Lymphocytes 660-1150/μL                   |                           |                               |                                   |              |
| Bégin, 2013  | P60        | Canada               | 0.6          | F   | Mitral valve insufficiency                           | ALC 600/μL                                | IgG 2340 mg/dL             | Normal haematopoiesis           | G-CSF 5 mcg/kg                    | NA           |
|              |            |                      |              |     | Prominent superficial venous                        | (1,500-2,800)                             | IgA 117 mg/dL              |                               | Prednisone Infliximab           |              |
|              |            |                      |              |     | IBD                                                  | T cell lymphopaenia                        | IgM 183 mg/dL              |                               |                                   |              |
|              |            |                      |              |     | Growth delay                                         |                                             |                           |                               |                                   |              |
| Estévez, 2013| P61       | Caucasian            | 11           | M   | Cryptorchidism                                       | ANC 45-1,200/μL                           | NA                        | G-CSF 5 mcg/kg/day              | Alive        |
|              |            |                      |              |     | Prominent superficial veins                         | Intermittent thrombocytopenia             |                           |                               |                                   |              |
| Alangeri, 2013| P62       | Saudi Arabia         | 12           | M   | Asthma                                               | ANC 7-500/μL                              | NA                        | Active trilineage haematopoiesis | G-CSF                 | NA           |
|              |            |                      |              |     | Bicuspid aortic valve Ingual hernia                 | Intermittent thrombocytopenia             |                           |                               | and no evidence of granulocytic arrest |              |
| Alangeri, 2013| P63       | Saudi Arabia         | 10           | F   | ASD Aphtous stomatitis Abdominal pain Asthma        | ANC 210/μL                               | NA                        | NA                            | NA                   | NA           |
|              |            |                      |              |     |                                                      | Intermittent thrombocytopenia             |                           |                               |                                   |              |
| Alangeri, 2013| P64       | Saudi Arabia         | NB           | M   | Septic shock                                        | NA                                        | NA                        | NA                            | NA                   | Deceased     |
| Alangeri, 2013| P65       | Saudi Arabia         | 9            | F   | Asthma                                               | ANC 110-600/μL                            | NA                        | No maturation arrest           | NA                   | NA           |
|              |            |                      |              |     |                                                      | Normal lymphocyte subset                 |                           |                               |                                   |              |
| Alangeri, 2013| P66       | Saudi Arabia         | 2            | M   | NA                                                   | ANC 180/μL                               | NA                        | Active granulopoiesis with no maturation arrest | G-CSF    | NA           |
|              |            |                      |              |     |                                                      |                                           |                           |                               |                                   |              |

(Continues)
| Author           | Individual | Country | Age (years) | Sex | Clinical remarks                                      | Cytopenias                  | Immunoglobulins          | Bone marrow | Treatment            | Outcome |
|------------------|------------|---------|-------------|-----|------------------------------------------------------|----------------------------|--------------------------|--------------|----------------------|---------|
| Arikoglu, 2014   | P67        | Turkey  | 3           | F   | ASD and PDA                                           | ANC 600/μL                 | IgG 889 mg/dL            | Normocellular marrow | G-CSF 5 mcg/kg | Alive   |
|                  |            |         |             |     | Frontal bossing                                      | Hb 6 g/dL                  |                          |                          |                      |         |
|                  |            |         |             |     | Depressed nasal bridge                               | Platelets 89000/μL         | IgA 50 mg/dL             |                          |                      |         |
|                  |            |         |             |     | Retrognathia                                          |                            | IgM 130 mg/dL            |                          |                      |         |
|                  |            |         |             |     | Prominent superficial venous pattern on chest and abdomen |                            | IgE <17 KU/L             |                          |                      |         |
|                  |            |         |             |     | Hepatomegaly                                          |                            | CD4+ T cells 260-436 mm³ |                          |                      |         |
|                  |            |         |             |     | Bilateral cortical renal cysts                        |                            | (500-2400)               |                          |                      |         |
|                  |            |         |             |     | PH                                                   |                            | CD19+ T cells 80-166 mm³ |                          |                      |         |
|                  |            |         |             |     |                                                      |                            | (200-2100)               |                          |                      |         |
| Kaya, 2014       | P68        | Turkey  | 0.4         | F   | Patent foramen ovale                                  | ANC 80/μL                  | Normal                   | Pegfilgrastim 100 mcg/kg | Alive   |
|                  |            |         |             |     | Minimal tricuspid insufficiency                        |                            | Normal                   |                          |                      |         |
|                  |            |         |             |     | Pancolitis, IBD                                       |                            | NA                       | Pegfilgrastim 100 mcg/kg | Alive   |
|                  |            |         |             |     |                                                      |                            | NA                       |                          |                      |         |
| Kaya, 2014       | P69        | Turkey  | 1           | F   | ASD                                                   | ANC 100/μL                 | NA                       | Pegfilgrastim 100 mcg/kg | Alive   |
|                  |            |         |             |     | Osteoporosis                                          |                            | NA                       |                          |                      |         |
| Desplantes, 2014 | P70        | France  | NB          | F   | Aortic insufficiency                                  | ANC 280/μL                 | NA                       | HSCT         | Alive           |         |
|                  |            |         |             |     | Grade III RVU, urethral duplication                    |                            | Mild thrombocytopenia Mild anaemia |                       |                      |         |
|                  |            |         |             |     | Prominent veins                                       |                            |                          |                          |                      |         |
|                  |            |         |             |     | Cutis laxa                                            |                            |                          |                          |                      |         |
|                  |            |         |             |     | Frontal bossing                                      |                            |                          |                          |                      |         |
|                  |            |         |             |     | Thick lips                                            |                            |                          |                          |                      |         |
|                  |            |         |             |     | Hypothyroidism                                        |                            |                          |                          |                      |         |
|                  |            |         |             |     | Neurodevelopment difficulties                         |                            |                          |                          |                      |         |
|                  |            |         |             |     | Leukaemia                                             |                            |                          |                          |                      |         |
| Desplantes, 2014 | P71        | France  | NB          | M   | ASD                                                   | ANC 383/μL                 | NA                       | G-CSF        | Deceased       |         |
|                  |            |         |             |     | Bilateral cryptorchidism                              |                            | NA                       |                          |                      |         |
|                  |            |         |             |     | Hypospadias                                           |                            | NA                       |                          |                      |         |
|                  |            |         |             |     | Prominent veins                                       |                            |                          |                          |                      |         |
|                  |            |         |             |     | Cutis laxa                                            |                            |                          |                          |                      |         |
|                  |            |         |             |     | Frontal bossing                                      |                            |                          |                          |                      |         |
|                  |            |         |             |     | Thick lips                                            |                            |                          |                          |                      |         |
|                  |            |         |             |     | Neurodevelopment difficulties                         |                            |                          |                          |                      |         |
TABLE 1 (Continued)

| Author      | Individual | Country | Age (years) | Sex | Clinical remarks                                      | Cytopenias          | Immunoglobulins | Bone marrow | Treatment | Outcome |
|-------------|------------|---------|-------------|-----|------------------------------------------------------|---------------------|----------------|-------------|-----------|---------|
| Desplantes, 2014 | P72        | France  | NB          | F   | ASD Bilateral grade I RVU Thrombocytopenia Mild anaemia | ANC 411/μL          | NA             | NA          | G-CSF     | Alive   |
|             |            |         |             |     | Prominent veins                                     |                     |                |             |           |         |
|             |            |         |             |     | Neurodevelopment                                     |                     |                |             |           |         |
|             |            |         |             |     | Difficulties                                         |                     |                |             |           |         |
| Desplantes, 2014 | P73        | France  | NB          | M   | PDA overriding aorta Grade III RVU Right cryptorchidism Prominent veins IBD | ANC 550/μL          | NA             | NA          | NA        | Deceased |
|             |            |         |             |     | Prominent veins                                      |                     |                |             |           |         |
|             |            |         |             |     | Neurodevelopment                                     |                     |                |             |           |         |
|             |            |         |             |     | Difficulties                                         |                     |                |             |           |         |
| Desplantes, 2014 | P74        | France  | NB          | M   | Cryptorchidism Bilateral RVU Megareter Prominent veins | ANC 314/μL          | NA             | NA          | G-CSF     | Alive   |
|             |            |         |             |     | Bilateral hearing loss Prominent lips Neurodevelopment |                     |                |             |           |         |
|             |            |         |             |     | Difficulties                                         |                     |                |             |           |         |
| Desplantes, 2014 | P75        | France  | 0.7         | M   | Prominent veins Kabuki syndrome like Cerebral palsy  | ANC 540/μL          | IgG 1870 mg/dL | NA          | G-CSF     | Alive   |
|             |            |         |             |     |                                                        |                     | (608-1229)     |             |           |         |
|             |            |         |             |     |                                                        |                     | IgA 170 mg/dL  |             |           |         |
|             |            |         |             |     |                                                        |                     | (33-200)       |             |           |         |
|             |            |         |             |     |                                                        |                     | IgM 170 mg/dL  |             |           |         |
|             |            |         |             |     |                                                        |                     | (46-197)       |             |           |         |
|             |            |         |             |     |                                                        |                     | CD3+ 1960      |             |           |         |
|             |            |         |             |     |                                                        |                     | (2100-6200)    |             |           |         |
|             |            |         |             |     |                                                        |                     | CD4+ 812       |             |           |         |
|             |            |         |             |     |                                                        |                     | (1300-3400)    |             |           |         |
|             |            |         |             |     |                                                        |                     | CD8+ 756       |             |           |         |
|             |            |         |             |     |                                                        |                     | (490-1300)     |             |           |         |
|             |            |         |             |     |                                                        |                     | CD19 364       |             |           |         |
|             |            |         |             |     |                                                        |                     | (390-1400)     |             |           |         |

(Continues)
| Author      | Individual | Country | Age (years) | Sex | Clinical remarks                                      | Cytopenias          | Immunoglobulins                | Bone marrow | Treatment     | Outcome |
|-------------|------------|---------|-------------|-----|-------------------------------------------------------|---------------------|--------------------------------|-------------|--------------|---------|
| Desplantes, 2014 | P76        | France  | NB          | M   | Aortic insufficiency Cryptorchidism Micropenis Prominent veins IBD Inguinal hernia | ANC 405/μL Mild thrombocytopenia Mild anaemia | NA                | NA          | G-CSF steroid | Alive  |
| Desplantes, 2014 | P77        | France  | NB          | M   | ASD Aortic insufficiency Cryptorchidism Prominent veins Umbilical hernia Frontal bossing | ANC 410/μL | IgG 435 mg/dL (332-1160) IgA 32 mg/dL (14-105) IgM 34 (45-190) CD3+ 1891 (2100-6200) CD4 1178 (1300-3400) CD8 682 (620-2000) CD19 651 (720-2600) | NA          | No treatment | Alive  |
| Desplantes, 2014 | P78        | France  | NB          | F   | Tricuspid regurgitation Bilateral RVU Bilateral deafness NA | ANC 400/μL | NA                | NA          | No treatment | Alive  |
| Desplantes, 2014 | P79        | France  | 0.7         | F   | ASD PH Broad nasal bridge | ANC 700/μL Severe anaemia | IgG 970 mg/dL (768-1630) IgA 170 mg/dL (68-378) IgM 100 mg/dL (60-230) CD3+ 378 (1200-2000) CD4+ 252 (530-1300) CD8+ 98 (330-920) CD19+ 49 (110-570) | NA          | G-CSF steroid | Alive  |
| Desplantes, 2014 | P80        | France  | NB          | F   | ASD Prominent veins | ANC 520/μL Severe thrombocytopenia Mild anaemia | NA                | NA          | G-CSF | Alive  |
| Desplantes, 2014 | P81        | France  | 4.5         | M   | ASD Cryptorchidism Prominent veins Delayed puberty | ANC 160/μL Mild anaemia | NA                | NA          | NA           | Deceased |
| Author                | Individual | Country | Age (years) | Sex | Clinical remarks                          | Cytopeanias                  | Immunoglobulins | Bone marrow | Treatment          | Outcome          |
|-----------------------|------------|---------|-------------|-----|------------------------------------------|----------------------------|-----------------|-------------|-------------------|-----------------|
| Desplantes, 2014      | P82        | France  | NB M        |     | Prominent veins                         | ANC 690/μL                    | IgG 560 mg/dL   | G-CSF       | Deceased          |                 |
|                       |            |         |             |     | Pierre Robin sequence                    | Mild thrombocytopenia         | (420-1090)      |             |                   |                 |
|                       |            |         |             |     | Major intellectual disability           | Mild anaemia                  | IgA 55 mg/dL    |             |                   |                 |
|                       |            |         |             |     |                                            | (22-157)                     | IgM 70 mg/dL    |             |                   |                 |
|                       |            |         |             |     |                                            | (45-263)                     | CD3+ 698 (1400-300) |             |                   |                 |
|                       |            |         |             |     |                                            | CD4+ 274 (700-2200)          | CD8+ 332 (490-1300) |             |                   |                 |
|                       |            |         |             |     |                                            | CD19+ 58 (390-1400)          |                |             |                   |                 |
| Notarangelo, 2014     | P83        | Italy   | 13 F        |     | Mitral valve prolapse                    | ANC 200/μL                    | IgG 1240 mg/dL  | G-CSF 5-10 mcg/kg/day | NA              |
|                       |            |         |             |     | Inguinal hernia                          | Mild anaemia                  | (231-947)       |             |                   |                 |
|                       |            |         |             |     | Hypergonadotropic hypogonadism           | Intermittent                   | IgA 54 mg/dL    |             |                   |                 |
|                       |            |         |             |     | Frontal bossing                          | thrombocytopenia               | (8-74)          |             |                   |                 |
|                       |            |         |             |     | Retrognathia                             |                               | IgM 79 (26-210) |             |                   |                 |
|                       |            |         |             |     | Prominent superficial venous pattern     |                               |                |             |                   |                 |
| Notarangelo, 2014     | P84        | Turkey  | 2 M         |     | Facial dysmorphisms                      | ANC 60/μL                     | IgG 974 mg/dL   | Delayed granulocyte maturation G-CSF 5 mcg/kg 3 times a week | NA              |
|                       |            |         |             |     | Prominent veins                          |                                | (462-1710)      |             |                   |                 |
|                       |            |         |             |     | Sensonineural hearing loss               |                                | IgA 64 mg/dL    |             |                   |                 |
|                       |            |         |             |     | Micropenis                                |                                | (27-173)        |             |                   |                 |
|                       |            |         |             |     | Coronal hypospadias                      |                                | IgM 118 mg/dL   |             |                   |                 |
|                       |            |         |             |     |                                            |                                | (62-257)        |             |                   |                 |
|                       |            |         |             |     | Delayed granulocyte maturation           | G-CSF 5 mcg/kg 3 times a week |                |             |                   |                 |
|                       |            |         |             |     |                                            |                               |                |             |                   |                 |
| Kiykim, 2015          | P85        | Turkey  | 19 M        |     | ASD                                      | ANC 500/μL                    | IgG 2520 mg/dL  | Hypercellular bone marrow and mild dysplasia in granulocytic lineage IVIG | Alive          |
|                       |            |         |             |     | Prominent superficial venous pattern     | ALC 400/μL                    | (913-1884)      |             |                   |                 |
|                       |            |         |             |     | Osteopenia                               |                                | IgM 89 mg/dL    |             |                   |                 |
|                       |            |         |             |     | Puberal delay                            |                                | (88-322)        |             |                   |                 |
|                       |            |         |             |     | BBD-like                                 |                                | IgA 67 mg/dL    |             |                   |                 |
|                       |            |         |             |     | Bronchiectasis                           |                                | (139-378)       |             |                   |                 |
|                       |            |         |             |     |                                            |                                | CD4+ T cells 124/μL |             |                   |                 |
|                       |            |         |             |     |                                            |                                | CD4+ T cells 140/μL |             |                   |                 |
|                       |            |         |             |     |                                            |                                | CD19 + 20 cells 20/μL |             |                   |                 |
|                       |            |         |             |     |                                            |                                | CD16+58 8/μL |             |                   |                 |

(Continues)
| Author            | Individual | Country    | Age (years)<sup>a</sup> | Sex<sup>b</sup> | Clinical remarks                                      | Cytopenias                        | Immunoglobulins | Bone marrow                              | Treatment               | Outcome  |
|-------------------|------------|------------|--------------------------|----------------|-------------------------------------------------------|-----------------------------------|----------------|------------------------------------------|------------------------|----------|
| Kiykim, 2015      | P86        | Turkey     | 11                       | F              | ASD and PDA                                          | ANC 300/μL                        | IgG 2000 mg/dL  | Hypercellular bone marrow: left shift in  | IVIG                   | Alive    |
|                   |            |            |                          |                | Osteoporosis                                         | ALC 1400/μL                      | (835-2894)    | granulopoiesis                          | G-CSF                   |          |
|                   |            |            |                          |                | Prominent superficial venous pattern                 |                                   | IgM 237 mg/dL   | Mild dysplasia in granulocytic lineage  | TMP-SMX                |          |
|                   |            |            |                          |                | Bronchiectasis                                       |                                   | (47-84)        |                                          |                        |          |
|                   |            |            |                          |                |                                                       |                                   | IgA 56 mg/dL   |                                          |                        |          |
|                   |            |            |                          |                |                                                       |                                   | (67-433)       |                                          |                        |          |
|                   |            |            |                          |                |                                                       |                                   |                |                                          |                        |          |
| Kiykim, 2015      | P87        | Turkey     | 16                       | F              | Mild mitral valve insufficiency                       | ANC 340/μL                        | IgG 1930 mg/dL | Mild dysplasia in granulocytic lineage  | IVIG                   | Alive    |
|                   |            |            |                          |                | Osteoporosis                                          | ALC 1700/μL                      | (667-2197)    |                                          | G-CSF                   |          |
|                   |            |            |                          |                | Pubertal delay                                        | CD19+20 85/μL                    | IgM 98 mg/dL   |                                          | TMP-SMX                |          |
|                   |            |            |                          |                | Bronchiectasis                                       | (75-448)                         | IgA 53 mg/dL   |                                          |                        |          |
|                   |            |            |                          |                |                                                       | (108-447)                        |                |                                          |                        |          |
|                   |            |            |                          |                |                                                       |                                   |                |                                          |                        |          |
| Mistry, 2017      | P88        | Great Britain| 12                       | M              | Arthritis                                            | Cyclic neutropenia                | Polyclonal increase in IgG and | No defect in neutrophil production or maturation | G-CSF for the first 20 years of life HSCT | Alive    |
|                   |            |            |                          |                | IBD-like                                              | Normocytic anaemia                | IgM            |                                          |                        |          |
|                   |            |            |                          |                |                                                       |                                   | (75-203)       |                                          |                        |          |
|                   |            |            |                          |                |                                                       |                                   | (67-162)       |                                          |                        |          |
|                   |            |            |                          |                |                                                       |                                   | (30-85)        |                                          |                        |          |
| Bolton, 2019      | P89        | Great Britain| 1.4                      | M              | IBD                                                   | Neutropenia                        | IgG 1660 mg/dL | Hypocellularity and maturation arrest of the myeloid development | G-CSF 5.22 mcg/kg/day HSCT | Deceased |
|                   |            |            |                          |                |                                                       | ALC 490/μL                        | (660-1200)    |                                          |                        |          |
|                   |            |            |                          |                |                                                       |                                   |                |                                          |                        |          |
| Case 1 (this report) | P90    | Mexico     | 0.3                      | M              | Low weight                                            | ANC 100-800/μL                    | IgG 398 mg/dL  | G-CSF 10 mcg/kg/day                       |                        | Deceased |
|                   |            |            |                          |                | Persistent foramen ovale                              | Intermittent thrombocytopenia     | (290-550)     |                                          |                        |          |
|                   |            |            |                          |                | PH                                                   | ALC 1400/μL                       | IgM 114 mg/dL  |                                          |                        |          |
|                   |            |            |                          |                | Bilateral hydro nephrosis                              |                                   | (30-85)        |                                          |                        |          |
|                   |            |            |                          |                | Prominent superficial veins in thorax, abdomen and limbs |                                   | IgA 44 mg/dL   |                                          |                        |          |
|                   |            |            |                          |                | Hepatomegaly                                          |                                   | (30-85)        |                                          |                        |          |
|                   |            |            |                          |                | Cryptorchidism                                        |                                   |                |                                          |                        |          |
|                   |            |            |                          |                | Velopalatal insufficiency                              |                                   |                |                                          |                        |          |
|                   |            |            |                          |                | Bilateral sensorineural hearing loss                   |                                   |                |                                          |                        |          |
|                   |            |            |                          |                |                                                       |                                   |                |                                          |                        |          |
| Case 2 (this report) | P91    | Mexico     | 15                       | F              | Bilateral sensorineural hearing loss                  | Intermittent neutropenia, nadir with 400/μL | IgG 396 mg/dL  | G-CSF 10 mcg/kg/day                       | Mesalazin  TMP-SMX Prednisone IVIG every 21 days | Deceased |
|                   |            |            |                          |                | IBD                                                   | ALC 1000/μL                       | (660-1220)    |                                          |                        |          |
|                   |            |            |                          |                | PH                                                   |                                   | IgA mg/dL      |                                          |                        |          |
|                   |            |            |                          |                | Prominent superficial veins                            |                                   | (56-203)       |                                          |                        |          |
|                   |            |            |                          |                | Mild tricuspid insufficiency                            |                                   | IgM 77 mg/dL   |                                          |                        |          |
|                   |            |            |                          |                | Puberal delay                                         |                                   | (57-162)       |                                          |                        |          |
|                   |            |            |                          |                |                                                       |                                   | IgE 36.6 mg/dL |                                          |                        |          |
| Author          | Individual | Country | Age (years)a | Sexb | Clinical remarks                                           | Cytopenias       | Immunoglobulins       | Bone marrow       | Treatment                        | Outcome |
|----------------|------------|---------|--------------|------|-----------------------------------------------------------|------------------|-----------------------|-------------------|---------------------------------|---------|
| Case 3 (this report) | P92        | Mexico  | 0.3          | F    | ASD and PDA Tricuspid insufficiency                       | ANC 200/μL      | IgG 2230 mg/dL (240-440) | Hypocellularity   | G-CSF 30 mcg/kg/ day             | Alive   |
|                 |            |         |              |      | Prominent superficial veins                               | ALC 1300/μL     | IgA 341 mg/dL (27-86)  |                  | TMP-SMX IVIG every 21 days       |         |
|                 |            |         |              |      | Bilateral sensorineural hearing loss                      |                  | IgM 77 mg/dL (34-114)  |                  |                                 |         |
|                 |            |         |              |      | Severe pulmonary damage                                   |                  |                       |                  |                                 |         |
|                 |            |         |              |      | PH                                                        |                  |                       |                  |                                 |         |
| Case 4 (this report) | P93        | Mexico  | 9            | M    | Persistent foramen ovale PH                               | ANC 450-790/μL  | NA                    | Cell hypoplasia   | G-CSF                           | Alive   |
|                 |            |         |              |      | Left inguinal hernia                                      |                   |                       |                  |                                 |         |
|                 |            |         |              |      | Prominent superficial veins                               |                   |                       |                  |                                 |         |
|                 |            |         |              |      | Redundant skin folds in neck                              |                   |                       |                  |                                 |         |
| Case 5 (this report) | P94        | Mexico  | 2            | F    | Bilateral conductive hearing loss                         | ANC 100/μL      | IgG 918 mg/dL (340-620) | Hypocellularity   | G-CSF 6 mcg/kg 4 days/week      | Alive   |
|                 |            |         |              |      | Intermittent lymphopaenia and thrombocytopenia             |                   | IgA 30.8 mg/dL (33-122) |                  |                                 |         |
|                 |            |         |              |      |                                                          |                   | IgM 81 mg/dL (48-143)  |                  |                                 |         |

**Abbreviations:** ALC, absolute lymphocyte count; ANC, absolute neutrophil count; ASD, atrial septal defect; G-CSF, granulocyte colony-stimulating factor; Hb, haemoglobin; HSCT, haematopoietic stem cell transplantation; IBD, inflammatory bowel disease; Ig, immunoglobulin; IVIG, intravenous gamma globulin; NB, newborn; PDA, persistent ductus arteriosus; PH, pulmonary hypertension; TMP-SMX, trimethoprim sulfamethoxazole.

aAge at diagnosis or follow up.
bF, female; M, male, NA, not available.
| Author | Individual | Country or ethnicity | Genotype | Protein change | Variant type | Syndromic |
|--------|------------|----------------------|----------|----------------|--------------|-----------|
| Boztug, 2009 | P1         | Turkey               | c.[758G>A] | p.[Arg253His] | Missense, homozygous | Yes |
| Boztug, 2009 | P2         | Turkey               | c.[758G>A] | p.[Arg253His] | Missense, homozygous | Yes |
| Boztug, 2009 | P3         | Turkey               | c.[758G>A] | p.[Arg253His] | Missense, homozygous | Yes |
| Boztug, 2009 | P4         | Turkey               | c.[758G>A] | p.[Arg253His] | Missense, homozygous | Yes |
| Boztug, 2009 | P5         | Turkey               | c.[758G>A] | p.[Arg253His] | Missense, homozygous | Yes |
| Boztug, 2009 | P6         | Turkey               | c.[554TT>C] | p.[Leu185Pro] | Missense, homozygous | Yes |
| Boztug, 2009 | P7         | Greece               | c.[141C>G] | p.[Tyr47Ter] | Nonsense, homozygous | Yes |
| Boztug, 2009 | P8         | Germany              | c.[778G>C] | p.[Gly260Arg] | Missense, homozygous | Yes |
| Boztug, 2009 | P9         | France               | c.[677 + 1G > A + 828C>T] | p.[ Tyr78Ter] + [Gln277Ter] | Insertion/Frameshift, compound heterozygous | Yes |
| Boztug, 2009 | P10        | Germany              | c.[784G>C] | p.[Gly260Arg] | Missense, homozygous | Yes |
| Boztug, 2009 | P11        | France               | c.[935_936insT] | p.[Asn313fs] | Insertion/Frameshift, compound heterozygous | Yes |
| Boztug, 2009 | P12        | Lebanon              | c.[144C>A] | p.[Tyr48Ter] | Nonsense, homozygous | Yes |
| Boztug, 2009 | P13        | Iran                 | c.[893_946delT] | p.[Glu295fs] | Frameshift, homozygous | Yes |
| Boztug, 2009 | P14        | Turkey               | c.[346A>C] | p.[Met116Val] | Missense, homozygous | Yes |
| Boztug, 2009 | P15        | Turkish              | c.[357delA] | p.[Ser255fs] | Small deletion/Frameshift, homozygous | Yes |
| Boztug, 2009 | P16        | Moroccan             | c.[346delA] | p.[Ser255fs] | Small deletion/Frameshift, homozygous | Yes |
| Boztug, 2009 | P17        | USA                  | c.[10delC] | NR             | NR          | No |
| Boztug, 2009 | P18        | USA                  | c.[10delC] | NR             | NR          | No |
| Boztug, 2009 | P19        | USA (Caucasian)      | c.[778G>C] | p.[Gly260Arg] | Missense, homozygous | Yes |
| McDermott, 2010 | P20     | USA (Caucasian)      | c.[778G>C] | p.[Gly260Arg] | Missense, homozygous | Yes |
| McDermott, 2010 | P21   | Turkish              | c.[347>T>G] | p.[Met116fs] | Frameshift, homozygous | Yes |
| McDermott, 2010 | P22   | Turkish              | c.[130C>T] | p.[Thr44fs] | Frameshift, homozygous | Yes |
| Eghbali, 2009 | P23        | Iran                 | c.[144C>A] | p.[Tyr48Ter] | Nonsense, homozygous | Yes |
| Xiu, 2009 | P24        | USA                  | c.[10delC] | NR             | NR          | No |
| Xiu, 2009 | P25        | USA                  | c.[10delC] | NR             | NR          | No |
| Hayes, 2011 | P26        | Pakistan             | c.[690_691insA] | p.[Thr232Argfs] | frameshift, homozygous | Yes |
| Hayes, 2011 | P27        | Pakistan             | c.[130C>T] | p.[Thr44fs] | Frameshift, homozygous | Yes |
| Cullinae, 2011 | P28       | Canada               | c.[756delA] | p.[Thr252fs] | Frameshift, homozygous | Yes |
| Banka, 2011 | P29        | Israel               | c.[758G>A] | p.[Arg253His] | Missense, homozygous | Yes |
| Banka, 2011 | P30        | Israel               | c.[758G>A] | p.[Arg253His] | Missense, homozygous | Yes |
| Banka, 2011 | P31        | Israel               | c.[758G>A] | p.[Arg253His] | Missense, homozygous | Yes |
| Alabdah, 2011 | P32       | Persian              | c.[144C>A] | p.[Tyr48Ter] | Nonsense, homozygous | Yes |
| Fernández, 2012 | P33      | Canada               | c.[829C>T] | p.[Thr277fs] | Frameshift, homozygous | Yes |
| Author, Year | Individual | Country or ethnicity | Genotype | Protein change | Variant type | Syndromic |
|-------------|------------|----------------------|----------|----------------|--------------|-----------|
| Smith, 2012 | P35        | Pakistan             | c.[190_210del] | p.[Thr64_Ile70del] | In-frame 21bp deletion, homozygous | Yes       |
| Smith, 2012 | P36        | Turkey               | c.[623T>G]   | p.[Leu208Arg]   | Missense, homozygous | No        |
| Smith, 2012 | P37        | Pakistan             | c.[130C>T]   | p.[Pro44Ser]    | Missense, homozygous | No        |
| Smith, 2012 | P38        | Pakistan             | c.[130C>T]   | p.[Pro44Ser]    | Missense, homozygous | No        |
| Boztug, 2012| P39        | Arab                 | c.[758G>A]   | p.[Arg253His]   | Missense, homozygous | Yes       |
| Boztug, 2012| P40        | Hispanic             | c.[210delC]+[348G>A] | p.[Ile70fsTer16]+[Gly260Arg] | SN insertion/frameshift +Missense (compound heterozygous) | Yes       |
| Boztug, 2012| P41        | Caucasian            | c.[758G>C]   | p.[Gly260Arg]   | Missense, homozygous | Yes       |
| Boztug, 2012| P42        | Caucasian            | c.[758G>C]   | p.[Gly260Arg]   | Missense, homozygous | Yes       |
| Boztug, 2012| P43        | Caucasian            | c.[482G>A]+[565C>T] | p.[Arg161Gln]+[Arg189Ter] | Missense + Nonsense, compound heterozygous | Yes       |
| Boztug, 2012| P44        | Hispanic             | c.[766_777delAG] | p.[Ser255fs]   | Frameshift, homozygous | Yes       |
| Boztug, 2012| P45        | Hispanic             | c.[210delC]+[348G>A] | p.[Ile70fsTer46]+[Met116Ile] | Frameshift, homozygous | Yes       |
| Boztug, 2012| P46        | Caucasian            | c.[677+1G>A]+[829>T] | p.[?] + [Gln277Ter] | Splice-site intronic +Nonsense, (compound heterozygous) | Yes       |
| Boztug, 2012| P47        | Persian              | c.[935dupT]  | p.[Asn3136]     | SN dup/Frameshift, homozygous | Yes       |
| Boztug, 2012| P48        | Hispanic             | c.[210delC]  | p.[Phe716Ter45] | SN deletion /Frameshift, homozygous | Yes       |
| Boztug, 2012| P49        | Hispanic             | c.[210delC]  | p.[Ile70fsTer4] | SN deletion /Frameshift, homozygous | Yes       |
| Boztug, 2012| P50        | Turkish              | c.[779G>A]   | p.[Gly260Asp]   | Missense, homozygous | Yes       |
| Boztug, 2012| P51        | Persian              | c.[416G>T]   | p.[Ser139Ile]   | Missense, homozygous | Yes       |
| Boztug, 2012| P52        | Caucasian            | c.[766_777delAG] | p.[Ser255fs]   | Frameshift, homozygous | Yes       |
| Boztug, 2012| P53        | Pakistani            | c.[131C>T]+[758G>A] | p.[Pro44Leu]+[Arg253His] | Missense, compound heterozygous | Yes       |
| Aytekin, 2013| P55       | Turkey               | c.[461T>C]   | p.[Leu154Pro]   | Missense, homozygous | Yes       |
| Banka, 2013 | P56        | Pakistan             | c.[347T>C]   | p.[Met116Thr]   | Missense, homozygous | No        |
| Banka, 2013 | P57        | Pakistan             | c.[347T>C]   | p.[Met116Thr]   | Missense, homozygous | No        |
| Banka, 2013 | P58        | Great Britain        | c.[757C>T]+[1000_1001] | p.[Arg253Cys]+[Met334fs] | Missense +Small deletion /Frameshift, compound heterozygous | No        |
| Banka, 2013 | P59        | Great Britain        | c.[757C>T]+[1000_1001] | p.[Arg253Cys]+[Met334fs] | Missense +Small deletion /Frameshift, compound heterozygous | No        |
| Bégin, 2013 | P60        | Canada               | c.[IVS3-1G>A]+[G778G>C] | p.[?] + [Gly260Arg] | Splice-site intronic +Missense, compound heterozygous | Yes       |
| Estévez, 2013| P61       | Caucasian            | c.[778G>C]   | p.[Gly260Arg]   | Missense, homozygous | Yes       |
| Alangeri, 2013| P62      | Saudi Arabia         | c.[974 T > G] | p.[Leu325Arg]   | Missense, homozygous | No        |
| Alangeri, 2013| P63      | Saudi Arabia         | c.[974 T > G] | p.[Leu325Arg]   | Missense, homozygous | No        |
| Alangeri, 2013| P64      | Saudi Arabia         | c.[974 T > G] | p.[Leu325Arg]   | Missense, homozygous | No        |
| Author            | Individual | Country or ethnicity | Genotype                         | Protein change       | Variant type               | Syndromic |
|-------------------|------------|----------------------|----------------------------------|----------------------|---------------------------|-----------|
| Alangeri, 2013    | P65        | Saudi Arabia         | c.[974 T > G]                     | p.[Leu325Arg]        | Missense, homozygous      | No        |
| Alangeri, 2013    | P66        | Saudi Arabia         | c.[974 T > G]                     | p.[Leu325Arg]        | Missense, homozygous      | No        |
| Arikoglu, 2014    | P67        | Turkey               | c.[175T>C]                        | p.[Trp59Arg]         | Missense, homozygous      | Yes       |
| Kaya, 2014        | P68        | Turkey               | c.[623T>C]                        | p.[Leu208Arg]        | Missense, homozygous      | No        |
| Kaya, 2014        | P69        | Turkey               | NR                               | NR                   | NR                        | No        |
| Desplantes, 2014  | P70        | France               | c.[249G>A]                        | p.[Trp83Ter]         | Nonsense, homozygous      | Yes       |
| Desplantes, 2014  | P71        | France               | c.[249G>A]                        | p.[Trp83Ter]         | Nonsense, homozygous      | Yes       |
| Desplantes, 2014  | P72        | France               | c.[249G>A]                        | p.[Trp83Ter]         | Nonsense, homozygous      | Yes       |
| Desplantes, 2014  | P73        | France               | c.[249G>A]                        | p.[Trp83Ter]         | Nonsense, homozygous      | Yes       |
| Desplantes, 2014  | P74        | France               | c.[249G>A]                        | p.[Trp83Ter]         | Nonsense, homozygous      | Yes       |
| Desplantes, 2014  | P75        | France               | c.[758G>A]                        | p.[Arg253His]        | Missense, homozygous      | Yes       |
| Desplantes, 2014  | P76        | France               | c.[481C>T]                        | p.[Arg161Ter]        | Nonsense, homozygous      | Yes       |
| Desplantes, 2014  | P77        | France               | c.[778G>C]                        | p.[Gly260Arg]        | Missense, homozygous      | Yes       |
| Desplantes, 2014  | P78        | France               | c.[778G>C]                        | p.[Gly260Arg]        | Missense, homozygous      | Yes       |
| Desplantes, 2014  | P79        | France               | c.[778G>C]                        | p.[Gly260Arg]        | Missense, homozygous      | Yes       |
| Desplantes, 2014  | P80        | France               | c.[565C>T]                        | p.[Arg189Ter]        | Nonsense, homozygous      | Yes       |
| Desplantes, 2014  | P81        | France               | c.[565C>T]                        | p.[Arg189Ter]        | Nonsense, homozygous      | Yes       |
| Desplantes, 2014  | P82        | France               | c.[565C>T]                        | p.[Arg189Ter]        | Nonsense, homozygous      | Yes       |
| Notarangelo, 2014 | P83        | Italy                | c.[144C>A]+[373_375delTAAT]       | p.[Tyr48Ter]+[Ile125del] | Nonsense + In-frame deletion, compound heterozygous | Yes |
| Notarangelo, 2014 | P84        | Turkey               | c.[680_684delinsT]                | p.[Ser227LeufsTer3]  | Indel/Frameshift, homozygous | Yes |
| Kiykim, 2015      | P85        | Turkey               | c.[535+1G>A]                      | NR                   | Splice-site intronic, homozygous | Yes |
| Kiykim, 2015      | P86        | Turkey               | c.[935dupT]                       | p.[Asn313fs]         | SN dup/frameshift, homozygous | Yes |
| Kiykim, 2015      | P87        | Turkey               | c.[C394T]                         | p.[Glu132Ter]        | Nonsense, homozygous      | Yes       |
| Mistry, 2017      | P88        | Great Britain        | c.[130C>T]                        | p.[Pro44Ser]         | Missense, homozygous      | Yes       |
| Bolton, 2019      | P89        | Great Britain        | c.[911dupC]                       | p.[Glu305fs82Ter]    | SN dup/frameshift, homozygous | No          |
| C1 (this report)  | P90        | Mexico               | c.[210delC]                       | p.[Phe71SerfsTer46]  | SN deletion/frameshift, homozygous | Yes |
| C2 (this report)  | P91        | Mexico               | c.[210delC]                       | p.[Phe71SerfsTer46]  | SN deletion/frameshift, homozygous | Yes |
| C3 (this report)  | P92        | Mexico               | c.[210delC]                       | p.[Phe71SerfsTer46]  | SN deletion/frameshift, homozygous | Yes |
| C4 (this report)  | P93        | Mexico               | c.[210delC] + [481C>T]            | p.[Phe71SerfsTer46] + [Arg161Ter] | SN deletion/frameshift + Nonsense (compound heterozygous) | Yes |
| C5 (this report)  | P94        | Mexico               | c.[210delC] + [421del]            | p.[Phe71SerfsTer46] + [Trp141GlyfsTer2] | SN deletion/frameshift, compound heterozygous | No |

Abbreviation: NR, not reported.
outcome was available for 79 patients, with survival at the time of publication of the original papers of 67/79 (84.8%) (Table 1).

Among the 94 reported patients, homozygous missense was the most frequent variant type (Table 2). Homozygous frameshift insertions, deletions, splice site or nonsense was also reported. Although the transition c.130C>T was associated with non-syndromic neutropenia in Pakistani patients, a genotype-phenotype correlation has not been confirmed.
Including our 5 patients, we describe a total of 94 patients with G6PC3. They frequently present with recurrent and severe bacterial infections during the first year of life, such as otitis media, skin abscesses, urinary tract infections, sino-pulmonary infections and sepsis. The diagnosis is suspected based on microbes (bacterial and fungal), infection sites (mouth, skin, bone, blood, lymph nodes, umbilical stump, respiratory and gastrointestinal tracts) and haematological findings: severe neutropenia was found in all reported patients; 37 patients had intermittent thrombocytopenia without clinical bleeding. Bone marrow aspirates of patients with G6PC3 deficiency showed a great diversity of findings, including: normocellular or hypercellular bone marrow, maturation arrest and even myelokathexis.7 So far, there is no evidence that G6PC3 deficiency is a preleukaemic condition. In this review, we found only 1 case of leukaemia (P70)8; no other reports of malignant transformation has been described in other SCN syndromes.5,9

We have been able to include here most of the patients reported in the medical literature, expanding the phenotype and describing the typical haematological and non-haematological features of G6PC3-deficient patients. The main limitations are the descriptive retrospective nature of the study, the fact that the information we rely upon is provided by different sources and authors, and lastly, the possibility of important data being lost throughout. Additionally, this is not a systematic review, and we are only including cases reported in English.

The activity of glucose-6-phosphatase is regulated by 3 genes: G6PC1, expressed in liver, small intestine and kidney, is related to the glycogenolytic and gluconeogenic pathways; G6PC2, expressed only in the pancreatic cells, is related to glucose level control; and G6PC3, ubiquitously expressed, hydrolyses glucose-6-phosphate to glucose in the final step of gluconeogenesis and glycogenolysis10 in the endoplasmic reticulum. G6PC3 is essential to control neutrophil viability3; its loss of function is associated with neutropenia due to an increase in endoplasmic reticulum stress and abnormal glucose homeostasis that leads to an increased susceptibility to apoptosis of neutrophils, skin fibroblasts and myeloid cells.11,12 The above findings suggest that G6PC3 deficiency is a quantitative and qualitative neutrophil disease.13

The immunological features are diverse and include T cell lymphopaenia, thymic hypoplasia and dysgammaglobulinaemia. Some articles suggest that the T cell lymphopaenia found in patients with G6PC3 deficiency may be associated with thymic hypoplasia. Nevertheless, the mechanisms leading to this thymic alteration are unclear.14 Some G6PC3-deficient patients may have a more profound immunological defect, and might require a deeper approach, including T cell flow cytometry and lymphoproliferation assays. When abnormalities in the function of T and B cells are demonstrated, it is mandatory to consider immunoglobulin replacement.9 Progressive lymphopaenia has also been reported; therefore, immunological long-term follow-up is required.

Non-haematological features are pivotal in differentiating G6PC3 deficiency from other causes of SCN:
structural heart defects, prominent superficial veins, urogenital malformations, growth retardation, pubertal and developmental delay. The phenotypic spectrum of the disease is expanding, as it might be syndromic or non-syndromic, the latter group being harder to diagnose given the absence of non-haematological features. In this review, 23/94 (24.4%) of the patients did not have any syndromic association. Thus, G6PC3 deficiency should be considered in any SCN of unknown aetiology.

The most frequent non-haematological features are cardiovascular malformations, atrial septal defect being the most common among those (55.3%). A wide range of cardiac abnormalities has been described in the literature, including heart valve abnormalities (mitral insufficiency, pulmonary valve stenosis, mitral and tricuspid insufficiency), followed by patent ductus arteriosus, coronary aneurysm, hypoplastic left ventricle and foramen ovale. The prominent superficial venous pattern was present in 58/94 (61.7%) of the patients reported, making it a frequent non-haematological feature. This alteration is less evident in childhood but becomes more prominent with age. These vascular changes have been attributed to increased cell apoptosis in myeloid cells, neutrophils and skin fibroblasts secondary to G6PC3 deficiency; as a consequence they can develop into varicose veins and ulcers during adulthood.

IBD has been reported in 10/94 reported patients with G6PC3 deficiency. Some authors suggest that autoinflammation through inflammasome activation may aggravate the IBD activity in G6PC3 deficiency. IBD is a common finding in phagocyte defects, such as chronic granulomatous disease and leucocyte adhesion deficiency; these patients show dysregulated and poorly controlled inflammation perpetuated by a breakdown in the mucosal homeostasis and defective bacterial recognition and clearance. Faecal calprotectin is not a good marker of inflammation in these patients since the neutropenia may give false-negative results; stool α1 antitrypsin may be a more reliable marker. Haematopoietic stem cell transplant is a reasonable alternative for severe gastrointestinal manifestations resistant to conventional treatments.

The treatment most frequently used was filgrastim (G-CSF), leading to an increase in the number of neutrophils, together with an improvement in the patient’s quality of life due to a decrease in the infection rate. In a murine G6PC3−/− model, G-CSF delayed, but did not prevent, neutrophil apoptosis. In that study, a 5-day G-CSF treatment regime corrected neutropenia, stimulated glucose uptake and improved neutrophil function. Depending on the severity of the defect, some patients received prophylactic antibiotics; mild phenotypes were treated with co-trimoxazole alone. On the other hand, more severe phenotypes may require G-CSF, antibiotics and gamma globulin replacement. In general, the reported survival is high, with a good quality of life as long as patients use filgrastim (G-CSF) and their malformations are surgically corrected. In recent years, therapeutic options other than G-CSF have emerged, such as SGLT2 inhibitor empagliflozin, a drug that decreases the concentration of 1,5-anhydroglucitol-6-phosphate (1,5AG6P), a toxic metabolite that accumulates in the plasma of G6PC3 patients; empagliflozin reduces the concentration of toxic metabolites allowing a recovery in neutrophil function.

This novel treatment appears promising, although further studies are needed. So far, there is no recommendation to endorse or promote HSCT as a definitive treatment for the neutropenia. In this review, only 3 patients underwent HSCT, of which 1 died due to complications associated with the procedure.

We recommend the use of filgrastim (G-CSF) in patients with recurrent or severe infections, as it is considered safe and improves neutrophil counts, prevents the recurrence of infections and it subjectively improved the quality of life in all reported cases. The dose and frequency of administration vary with the needs of each patient. We also recommend the use of oral ambulatory prophylactic antibiotics; co-trimoxazole is a cheap and safe choice to diminish the rate and severity of infections, particularly in countries where the access to G-CSF is limited. A small group of patients has a higher immune compromise, so we suggest that all patients who either continue to suffer recurrent infections despite having normal levels of neutrophils or who have persistent lymphopenia should be further evaluated with immunoglobulin levels testing, flow cytometry and lymphoproliferation assays. So far, HSCT is only suggested in patients with IBD refractory to conventional pharmacological treatment and in patients with G-CSF refractory disease (G-CSF dose >50 μg/kg/day or myelodysplastic syndrome). HSCT is not routinely recommended, with most reports showing a good evolution with the exclusive use of filgrastim (G-CSF) and surgery to treat malformations.

Although G6PC3 deficiency is a rare disease, there is an increasing number of case reports around the world. This allows us to have a clearer idea of the clinical picture, the associated syndromic features and the best treatment for these patients. Given a clinical suspicion of G6PC3, it is appropriate to carry out a complete medical history that includes consanguinity, type and number of infections and microbiological isolates. An exhaustive physical examination is mandatory, searching for a triangular face, depressed nasal bridge, redundant neck skin, cutis laxa, prominent veins, cardiac murmur, overlapping toes and urogenital malformations, as they may be present in the syndromic phenotype.
All patients with suspected G6PC3 deficiency should have an echocardiogram and renal ultrasound. They must also have a close monitoring of weight, height and growth velocity, with any alteration prompting measurements of growth hormone levels and an evaluation by an endocrinologist. Although it is an infrequent manifestation, the presence of loose stools or bloody diarrhoea, tenesmus or abdominal pain suggests IBD. These patients should be evaluated with a complete blood count, erythrocyte sedimentation rate or C-reactive protein, albumin, faecal calprotectin and upper endoscopy/colonoscopy with biopsies.

The c.210delC variant was present in all five Mexican patients from this report and in most Hispanic patients reported to date. Banka and Newman\(^1^7\) pointed out there might be some founder effects: Arg253His is frequent in the Middle East, Gly260Arg is more frequent in Caucasians from Europe and Phe71SerfsTer46 (c.210delC) is common among unrelated individuals of Hispanic descent. With a frequency of 0.00011 in gnomAD (gnomad.broadinstitute.org/variant/17-42148542-TC-T?dataset=gnomad_r2_1), all 28 existing alleles (16 women and 12 men, all heterozygous) are from Latino/Admixed American individuals. Our 5 patients came from different regions of the country, mostly from Central and North Mexico. Although there was no known history of consanguinity, endogamy at small, geographically isolated communities might explain the homozygosity in three of the families.

There are multiple unanswered questions about G6PC3-deficient patients. The cause for the heterogeneity of the bone marrow findings is currently unknown, as is the reason why some patients present with thymic hypoplasia, lymphopaenia and hypogammaglobulinaemia. Whether the neurodevelopmental delay and hearing loss described in some patients are caused by prolonged hospitalizations and recurrent infections, or they are part of the disease phenotype, is also unclear. Other exceptional clinical features, such as oculocutaneous albinism, might result from different autosomal recessive gene defects in highly consanguineous populations.

In conclusion, we described five and reviewed 89 more cases of G6PC3 deficiency reported in the literature during the last 10 years, including clinical features, treatment, prognosis and mutational analysis. It is a disease with a high heterogeneity, with syndromic and non-syndromic phenotypes. A possible G6PC3 deficiency should be considered in every patient with severe congenital neutropenia. The follow-up should include growth and development evaluation, as well as an assessment of complete blood count, echocardiogram and renal ultrasound, while individualizing the needs of each patient, as clinical penetrance is variable, and no genotype-phenotype has been described. The ongoing management of the disease should be conducted within a multidisciplinary team. We recommend treating with G-CSF and antibiotic prophylaxis, as they seem to improve the frequency of infections and quality of life. An increasing number of cases of G6PC3 deficiency in the world is likely to continue to be identified due to easier access to diagnostic methods, expanding our understanding of this disease.

**CONFLICT OF INTEREST**

APG works as medical manager at Glaxo-Smith Kline. GMCS used to be a medical advisor for Astra Zeneca. None related to this study.

**AUTHOR CONTRIBUTIONS**

Substantial contribution to the acquisition of the data was provided by N Velez-Tirado, MA Yamazaki-Nakashimada, E Lopez Valentín, A Partida-Gaytan, SC Scheffler-Mendoza, GM Chaia Semerena, A Alvarez-Cardona and MA Suárez Gutiérrez, who also suspected the diagnosis and cared for the patients. Substantial contributions to the conception of the work, analysis of the data and drafting of the manuscript were provided by N Velez-Tirado, MA Yamazaki Nakashimada and SO. Lugo Reyes. Substantial contribution to laboratory and genetic diagnoses were provided by EA Medina-Torres, P Baeza-Capetillo, THirschmugl, W Garncarz, SE Espinosa-Padilla, JA Aguirre Hernández, C Klein and K Boztug, who also revised the manuscript critically. All authors read and approved the final manuscript.

**DATA AVAILABILITY STATEMENT**

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

**ORCID**

Natalia Velez-Tirado 🐦 https://orcid.org/0000-0002-2936-3679

Saul O. Lugo Reyes 🐦 https://orcid.org/0000-0002-3730-4150

**REFERENCES**

1. Sullivan KE, Stiehm ER. Common presentations and diagnostic approaches. In: Sullivan KE, Stiehm R, eds. *Stiehm's Immune Deficiencies* (2nd edn). Elsevier; 2020: 1332. Available from: https://www.elsevier.com/books/stiehms-immune-deficiencies/sullivan/978-0-12-816768-7 Accessed February 17, 2021.

2. Klein C. Kostmann’s disease and HCLSI-associated protein X-1 (HAX1). *J Clin Immunol.* 2017;37(2):117-122. doi:10.1007/s10875-016-0358-2

3. Boztug K, Appaswamy G, Sc M, et al. A novel syndrome with congenital neutropenia caused by mutations in G6PC3. *N Engl J Med.* 2009;360(1):32-43.
4. Dursun A, Ozgul RK, Soydas A, et al. Familial pulmonary arterial hypertension, leucopenia, and atrial septal defect: a probable new familial syndrome with multisystem involvement. Clin Dysmorphol. 2009;18(1):19-23. doi:10.1097/MCD.0b013e32831841f7

5. Boztug K, Rosenberg PS, Dorda M, et al. Extended spectrum of human glucose-6-phosphatase catalytic subunit 3 deficiency: novel genotypes and phenotypic variability in severe congenital neutropenia. J Pediatr. 2012;160(4):679-683.e2.

6. Xia J, Bolyard AA, Rodger E, et al. Prevalence of mutations in ELANE, GFI1, HAX1, SBDS, WAS and G6PC3 in patients with severe congenital neutropenia. Br J Haematol. 2009;147(4):535-542.

7. Banka S, Wynn R, Newman WG. Variability of bone marrow morphology in G6PC3 mutations: is there a genotype-phenotype correlation or age-dependent relationship? Am J Hematol. 2011;86(2):235-237.

8. Desplantes C, Fremont ML, Beaupain B, et al. Clinical spectrum and long-term follow-up of 14 cases with G6PC3 mutations from the French severe congenital neutropenia registry. Orphanet J Rare Dis. 2014;9(1):1-15.

9. Kiykim A, Baris S, Karakoc-Aydiner E, et al. G6PC3 deficiency. J Pediatr Hematol Oncol. 2015;37(8):616-622.

10. Aytekin C, Germeshausen M, Tuygun N, Dogu F, Ikinciogullari A. A novel G6PC3 gene mutation in a patient with severe congenital neutropenia. J Pediatr Hematol Oncol. 2013;35(2):2012-2014.

11. Banka S, Chervinsky E, Newman WG, et al. Further delineation of the phenotype of severe congenital neutropenia type 4 due to mutations in G6PC3. Eur J Hum Genet. 2011;19(1):18-22.

12. Bolton C, Burch N, Morgan J, et al. Remission of inflammatory bowel disease in glucose-6-phosphatase 3 deficiency by allogeneic haematopoietic stem cell transplantation. J Crohn's Colitis. 2020;14(1):142-147.

13. Boztug K, Klein C. Genetics and pathophysiology of severe congenital neutropenia syndromes unrelated to neutrophil elastase. Hematol Oncol Clin North Am. 2013;27(1):43-60.

14. Bégin P, Patey N, Mueller F, et al. Inflammatory bowel disease and T cell lymphopenia in G6PC3 deficiency. J Clin Immunol. 2013;33(3):520-525.

15. Eghbali A, Eshghi P, Malek F, Rezaei N. Cardiac and renal malformations in a patient with sepsis and severe congenital neutropenia. Iran J Pediatr. 2010;20(2):225-228.

16. Banka S, Wynn R, Byers H, Arkwright PD, Newman WG. G6PC3 mutations cause non-syndromic severe congenital neutropenia. Mol Genet Metab. 2013;108(2):138-141.

17. Banka S, Newman WG. A clinical and molecular review of ubiquitous glucose-6-phosphatase deficiency caused by G6PC3 mutations. Orphanet J Rare Dis. 2013;8(1):84.

18. Chiriac M, Salfa I, Di Matteo G, Rossi P, Finocchi A. Chronic granulomatous disease: clinical, molecular, and therapeutic aspects. Pediatr Allergy Immunol. 2016;27(3):242-253.

19. Mistry A, Scambler T, Parry D, et al. Glucose-6-phosphatase catalytic subunit 3 (G6PC3) deficiency associated with autoinflammatory complications. Front Immunol. 2017;8:1-7.

20. Kelsen JR, Sullivan KE, Rabizadeh S, et al. NASPGHAN position paper on the evaluation and management for patients with very early-onset inflammatory bowel disease (VEO-IBD). Intergovernmental panel on climate change, editor. J Pediatr Gastroenterol Nutr. 2019;53(9):1.

21. Goenka A, Doherty JA, Al-Farsi T, et al. Neutrophil dysfunction triggers inflammatory bowel disease in G6PC3 deficiency. J Leukoc Biol. 2021;109(6):1147-1154.

22. Kaya Z, Eğirtaş O, Albayrak M, et al. Resolution of inflammatory colitis with pegfilgrastim treatment in a case of severe congenital neutropenia due to glucose 6 phosphatase catalytic subunit-3 deficiency. J Pediatr Hematol Oncol. 2014;36(5):316-318.

23. Sik Jun H, Mok Lee Y, Duk Song K, Mansfield BC, Chou YJ. G-CSF improves murine G6PC3-deficient neutrophil function by modulating. Blood. 2011;117(14):3881-3892.

24. Veiga-da-Cunha M, Chevalier N, Stephenne X, et al. Failure to eliminate a phosphorylated glucose analog leads to neutropenia in patients with G6PT and G6PC3 deficiency. Proc Natl Acad Sci. 2019;116(4):1241-1250.

25. Wortmann S, Van Hove J, Derks T, et al. Traeung neutropenia and neutrophil dysfunction in glycogen storage disease type Ib with an SGLT2 inhibitor. Blood. 2020;136(9):1033-1043.

How to cite this article: Velez-Tirado N, Yamazaki-Nakashimada MA, Lopez Valentín E, et al. Severe congenital neutropenia due to G6PC3 deficiency: Case series of five patients and literature review. Scand J Immunol. 2022;95:e13136. doi:10.1111/sji.13136