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Original Article

Congenital Cardiac Defects in G6PC3 Deficiency: Report of a Mutation and a Literature Review

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Abstract

Background: Congenital cardiac anomalies are considered the most frequent non-hematologic manifestation of Glucose-6-phosphatase 3 (G6PC3) deficiency.

Methods: We report a case of G6PC3-deficiency with a novel homozygous frameshift variant (c.911dupC; p.Gln305SerfsTer82), who developed intermittent neutropenia and was diagnosed long after a repair cardiac surgery for patent ductus arteriosus (PDA). To further investigate the importance of immunologic workups in patients with congenital cardiac defects, we provide a literature review on the observed cardiac findings in patients with SCN4.

Results: Overall, 78.3% of reported patients had cardiac defects, with more than half of the patients (56%) presenting with ASD. More than half of the patients with ASD required surgical repair, which implies the severity of symptoms.

Conclusion: These findings highlight the importance of performing immunologic work-ups in children initially manifesting congenital heart defects. A simple differential cell-blood-count test may prevent future life-threatening disseminated infections, especially in countries with high rates of consanguinity and, subsequently, higher prevalence of primary immunodeficiencies.

Keywords: G6PC3; CGD; Heart Defects; ASD; Neutropenia

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Introduction

Glucose-6-phosphatase 3 (G6PC3) deficiency or severe congenital neutropenia type 4 (SCN4), OMIM: 612541, is an allelic heterogeneous inherited immune deficiency causing impaired activity of G6PC3 (1, 2). Mutations in the *G6PC3* gene cause impaired myeloid differentiation, resulting in neutropenia with defective respiratory burst, chemotaxis, and ROS production (1, 3). Patients usually present with recurrent bacterial infections at early ages. In contrast to other genetic SCN variants, patients with SCN4 are unlikely to develop leukemic or myelodysplastic features (4, 5). This group of SCNs may develop intermittent

thrombocytopenia and lymphopenia in addition to the expected neutropenia (6). Patients usually harbor syndromic features, including congenital heart defects, urogenital anomalies, superficial venous angiectasia, and deafness (1); however, some patients may not develop any of the syndromic features (7). The most frequent non-hematologic manifestation of patients with G6PC3 deficiency is congenital cardiac anomaly esp. atrial septal defect (ASD)(3). Most cardiac defects are severe enough to undergo surgical repair (8). Thus far, no phenotype-genotype association is reported in patients with SCN4 except for a hypothetical relationship between the non-syndromic features and c.130 C>T variant (9). Nevertheless, cardiac defects have not been reported to be more prevalent in certain mutations (3, 5).

Given the single locus affected in SCN4, the variety in phenotypic features is not seemingly attributed to a multifactorial or mutagenic setting. Therefore, addressing the role of the defective enzyme in cardiac system development is pivotal for targeting the disease properly. However, data on the association between G6PC3 and cardiac system development is sparse.

Herein, we report a case of a 2-year-old female patient from a consanguineous background diagnosed with SCN4, who harbored a novel frameshift mutation in the 6th exon. She developed intermittent neutropenia and the diagnosis of SCN was made long after a repair cardiac surgery for patent ductus arteriosus (PDA). She also had ASD secundum and partial anomalous pulmonary vein connection (PAPVC). To further investigate the importance of immunologic workups for patients with congenital cardiac defects, we provided a literature review on the observed cardiac findings in patients with SCN4.

Case Presentation

A 25-month-old girl was admitted due to hypotonia, recurrent transient apnea, and cyanosis shortly after breastfeeding. On chest radiography, cardiomegaly and prominent pulmonary vasculature were noted. Echocardiography was performed, revealing a large PDA and a large ASD secundum with bidirectional shunt along with severe pulmonary hypertension (PH) and moderate pulmonary insufficiency (PI). Due to symptomatic ASD, she underwent a PDA closure surgery. Surgeons reported a large PDA resembling the aortic arch, which was repaired through triple ligation and transfixion. Post-op echocardiography showed a tiny residual PDA. During this admission, she initially had pancytopenia, which resolved shortly after **(Table 1).**

Two months later, she was referred to our center with fever, respiratory distress, poor feeding, and hypotonia. Control echocardiography revealed large ASD with mild PH, right ventricular hypertrophy (RVH), right atrial enlargement (RAE), dilated main pulmonary artery (MPA), and no residual PDA. Gastroesophageal reflux was detected in barium swallow. The obtained EEG was normal. The patient was treated with IV antibiotic therapy, and the fever was resolved. Thus, symptoms were assigned to the ongoing cardiac defect with pulmonary hypertension, and she was discharged on Sildenafil and Lasix. A month later, she was readmitted due to aggravating respiratory distress, cough, recurrent vomiting, and severe failure to thrive (FTT). Chest radiography showed cardiomegaly with prominent pulmonary trunk and pulmonary vasculature. TORCH serologies were positive for CMV IgG and IgM, and a positive blood culture for Pseudomonas aeruginosa was detected. Sweat test results were negative for Cystic fibrosis. In order to relieve her symptoms, a percutaneous endoscopic gastrostomy (PEG) was placed for nutritional aid. For the first time, an immunology consult was done due to leukopenia, and a complete primary immunodeficiency workup plus bone marrow aspiration was requested. Unfortunately, the patient was discharged with her parents' personal consent. Three months later, she was readmitted with similar symptoms. A cardiac catheterization was performed to evaluate PH. Due to her young age, it was preferred that the patient be followed up on Sildenafil. An immunological consult suggested the diagnosis of congenital neutropenia, and subcutaneous G-CSF injections three times weekly were started. She was under regular follow-up and symptom-free for the next two years.

Once again she was admitted due to productive cough and respiratory distress and the impression of atypical pneumonia. This time, her symptoms subsided with Azithromycin. A year later, at the age of 4 years, she developed severe headaches with confusion. A Brain CT scan revealed an ab-

Table 1. Cell blood counts of the patient in frequent admissions

Test	Value					Unit	Normal range
WBC	1870-4510	3480-1700	2460-2930	6000	900-23390	/µl	5000 to 17000
Neutrophils	900-2670	1980-650	1090-470	2340	20-7590	/µl	1500 to 8500
Hemoglobin	10-11.2	12.8-9	10.7-10.9	13	12	mg/dL	11.5 to 13.5
Platelet	130/530	263/193	163/203	192	340	/µl	150 to 450

scess in the right frontal lobe with a midline shift. The abscess was drained surgically and confirmed to be due to Aspergillosis (*aspergillus fumigatus*). She had no complications with combined antibiotic and antifungal treatment. Ten months later, she developed a fever and productive cough and was treated with IV Ceftriaxone due to the impression of bacterial pneumonia. Control brain CT scan revealed focal encephalomalacia changes and a hole defect in frontal lobe. No evidence of a midline shift and hemorrhage were observed. This time, in echocardiography, besides the large 2 cm ASD causing a single atrium, anomalous pulmonary veins draining to SVC were evident. Regarding the PAPVC and her proper age for the operation, she underwent repair surgery two months later. During this surgery, ASD and PAPVC were repaired with the Warden Technique with total thymectomy. She was symptom-free for the next 12 months on G-CSF therapy. Whole exome sequencing revealed a homozygous frameshift variant in the *G6PC3* gene, c.911dupC, leading to p.Gln305 SerfsTer82.

Discussion

Aside from the novel mutation identified in this patient, the intermittent neutropenia and the severe cardiac defects leading to the late diagnosis of G6PC3 deficiency were noteworthy findings in this patient. Severe cardiac defects in patients with G6PC3 deficiency can mask the immunodeficiency and delay rapid diagnosis. Although the proper treatment for cardiac defects is distinct from the resolution of immunodeficiency, severe congenital heart defects highlight the importance of immune status evaluation or at least neutrophil functional tests in children. To further address the association between congenital defects and neutropenia, we have reviewed the previous reports of patients with G6PC3 deficiency.

Studies reported the most common cardiac defects to be ASD, PDA, followed by primary pulmonary hypertension (PPH) and valvular anomalies (8, 9). Banka *et al.* reviewed the clinical presentations of 57 patients with G6PC3 deficiency reported up to June 2013 (3).

We have conducted a literature review of patients reported since 2013. In this brief review illustrated in **Table 2**, a total number of 39 patients were included, out of whom seven patients had normal cardiac examinations. We found the most frequent cardiac presentations to be ASD (15/39), followed by aortic insufficiency (AI), PDA, patent foramen ovale (PFO), TR, and PH. Overall, 78.3% of reported patients up until now had cardiac defects, with more than half of the patients (56%) presenting with ASD. More than half of the patients with ASD required surgical repair, which implies the severity of symptoms. The reported congenital defects and genomic variants are represented in **Table 3.** There was no association between gender and cardiac defect presentation in patients with SCN4, with 80% of reported male patients and 76.9% of female patients presenting with cardiac defects. According to this literature review, the diagnosis of SCN4 has been made above 10 years of age in 41.5% of patients, further implying the severity of non-immunologic presentations compared to the immunodeficiency. Furthermore, there was no association between reported mutations and the presence of cardiac defects **(Table 3).**

Conclusion

Non-hematologic features in G6PC3 deficiency, such as developmental cardiac anomalies, are common. It is important that all subspecialties, from pediatric cardiology to pediatric nephrology, are involved early in the care of affected children. Our case illustrates that delay in diagnosis and therapy is disadvantageous. National and international patient registries are required to design evidence-based, multidisciplinary guidelines for the early detection of these disorders.

Table 2. Literature review of reported features in patients with SCN4.

#	Ref.	Year	Originality	Mutation	Protein	Age	Sex	Cardiac manifestation	Manifestations	Treatment	Outcome
1	[7]	2017	Pakistani	c.130 C>T	p.(Pro44Ser)	12 y	M	None	oral aphthous ulcers, perianal ulceration, oligoarthritis, cervical lymphadenopathy, erythema nodosum, paronychial nail infections 2and conjunctival herpes virus infection	Prednisolone, adalimumab	Corticosteroid-dependant, responded well to adalimumab
2	[7]	2017	Pakistani	c.130 C>T	p.(Pro44Ser)	?	M	None	Same manifestations of his older sibling but milder		
3	[10]	2014	Italian	c.373_375 delAAT	p.I125del	20 y	F	MVP	skin infection, pulmonary abscess, brain abscess, delayed puberty, facial dysmorphism, superficial venous pattern of the lower limbs	G-CSF	Symptom-free in 12 years on G-CSF
4	[10]	2014	Turkish	c.680_684 delinsT	p.S227Lfs*3	2	M	None	otitis, parotitis, S. viridans sepsis, S. aureus gluteal abscess, and recurrent aphtous stomatitis, Mild sensorineural hearing loss, facial dysmorphism, prominent superficial venous pattern on the arms, legs and trunk, and micropenis with coronal ipospadia	G-CSF	Infection-free for one year F/U
5	[8]	2014	French	c.[249G > A]	p.[W83*]	New born	F	Aortic insufficiency	Prominent veins, Heart failure, Respiratory failure Hypothyroidism, facial dysmorphism, Grade III RVU, urethral duplication	Sibling 5 HSCT	AML at the age of 14- alive to 36 years
6	[8]	2014	French	c.[249G > A]	p.[W83*]	New born	M	ASD/surgery	Prominent veins, facial dysmorphism, Hypospadias, Bilateral cryptorchidism	Sibling 1 G-CSF	Died at 17
7	[8]	2014	French	c.[249G > A]	p.[W83*]	New born	F	ASD/surgery	Prominent veins, Respiratory failure, facial dysmorphism, Bilateral grade I RV	Sibling 2 G-CSF	Alive to 29
8	[8]	2014	French	c.[249G > A]	p.[W83*]	New born	M	PDA Overriding aorta	Prominent veins, Pulmonary arterial hypertension Polyarthritis, facial dysmorphism, Grade III RVU right side Cryptorchidism 9	Sibling 3 No Tx	Died at 30 (Sudden death)
9	[8]	2014	French	c.[249G > A]	p.[W83*]	New born	M	WPW Sd	P10rominent veins, Bilateral hearing loss, Congenital right ptosis, facial dysmorphism, Cryptorchidism, Megaureter, Bilateral RVU	Sibling 4 G-CSF	Alive to 24
10	[8]	2014	French	c.[758G > A]	p.[R253H]	7 months	M	None	Prominent veins, Kabuki syndrome like, Portal cavernoma, Cerebral palsy	G-CSF	Alive to 13
11	[8]	2014	French	c.[829C > T]	p.[Q277*]	New born	F	Mild dilatation of ascendant aorta	Prominent veins, Myopathy Polyarthritis, Raynaud Hyperopia, Gastroesophageal reflux urinary incontinence, Loose stools	G-CSF	Alive to 19
12	[8]	2014	French	c.[481C > T]	p.[R161*]	New born	M	Aortic insufficiency	Prominent veins, Narrowed thorax, IBD, Inguinal hernia, Cryptorchidism	G-CSF	Alive to 17
13	[8]	2014	French	c.[778G > C]	p.[G260R]	New born	M	ASD Aortic insufficiency Tricuspid regurgitation/surgery	Prominent veins, light strabism Umbilical hernia, Bilateral deafness, facial dysmorphism, Bilateral RVU	Sibling 1 No Tx	Alive to 16
14	[8]	2014	French	c.[778G > C]	p.[G260R]	New born	F	ASD Primary pulmonary hypertension	facial dysmorphism	Sibling 2 No Tx	Alive to 3

Table 2. Continued

15	[8]	2014	French	c.[778G > C]	p.[G260R]	7 months	F	ASD/surgery	Prominent veins, HTAP, dwarfism, Deafness		G-CSF, LD steroids	Alive to 50
16	[8]	2014	French	c.[565C > T]	p.[R189*]	New born	F	ASD/surgery	Prominent veins, very high voice,	Sibling 1	G-CSF	Alive to 29
17	[8]	2014	French	c.[565C > T]	p.[R189*]	4.5 Y	M	ASD/surgery Death/sudden death after sport activity	Prominent veins, Precocious pubic hair growth and delayed puberty, Cryptorchidism	Sibling 2	No	Died at 30
18	[8]	2014	French	c.[565C > T]	p.[R189*	New born	M	None	Prominent veins, Pierre robin sequence, Brachiocephalic thrombosis, failure to thrive Enteral nutrition gastrostomy, Major intellectual disability with bilateral sus-tentorial atrophy on MRI		G-CSF	Died at 5
19	[11]	2016	Dominican Republic	c.218 + 1G > A	p.W73X	12 y	M	Repaired ASD	FTT, and recurrent mouth sores, orchiectomy for an undescended testicle, and repair of an inguinal hernia, prominent superficial vasculature of the upper extremities and chest, mild dysmorphic facial features, facial cellulitis		GCSF	Symptom-free for 2 years
20	[11]	2016	Dominican Republic	c.218 + 1G > A	p.W73X	17 y	M	NA	distal ileal stricture associated with an arteriovenous malformation, FTT, dysmorphic facial features, osteoporosis, recurrent oral ulcers, and cryptorchidism, recurrent cellulitis, H. pylori gastritis, and C. difficile colitis		GCSF	Responded well to G-CSF
21	[11]	2016	Dominican Republic	c.218 + 1G > A	p.W73X	4y	M	repaired ASD	Poland Syndrome, dysmorphic facial features, aspiration pneumonia, FTT, pulmonary hypertension, chronic lung disease, gastroesophageal reflux, prominent superficial veins of his upper and lower extremities and chest disease, and developmental delay, bilateral inguinal hernia repair, vesicoureteral reflux repair,		GCSF	Recurring respiratory viral illnesses, skin infections leading to septic shock
22	[12]	2016	Turkey	c.141 C>G	Y47X	New born	M	None	bilateral undescended testicles and prominent superficial veins, (ANC 0)		GCSF	Symptom-free until 6 months of age
23	[6]	2015	Turkey	c.535+ 1G> A	p.?	19	M	ASD type II	Osteoporosis Pubertal delay, Bronchiectasis, no UG ability, recurrent respiratory tract infections, otitis, and diarrhea since infancy, delayed growth and pubertal development, digital clubbing, splenomegaly, prominent superficial venous pattern		IVIG TMP-SMX Azathiopurine Mesalazine Testosterone	frequency and severity of infections were decreased
24	[6]	2015	Turkey	c. 935 dupT	p. Asn313fs	11	F	ASD, PDA	recurrent pneumonia and otitis, recurrent skin abscesses, aphtous stomatitis, suppurative otitis media, Osteopenia, Nephrolithiasis, Bronchiectasis, Cholecystolithiasis Sensorineural hearing loss, FTT, digital clubbing, prominent superficial venous pattern, hepatosplenomegaly		IVIG G-CSF TMP-SMX	Partial response
25	[6]	2015	Turkey	c. C394T	p. Q132X	16	F	Mild mitral valve insufficiency	diarrhea, developmental delay, recurrent respiratory infections and otitis media, oral ulcers, Bronchiectasis Sensorineural hearing loss, Osteoporosis Pubertal delay Hypothyroidism, No GU abnlity, visible superficial venous pattern on the skin		IVIG TMP-SMX	failed to respond to G-CSF

Table 2. Continued

26	[4]	2015	Arab	c.758G>A	Arg253His	66	M	PFO	choroid plexus cyst, enlarged brain ventricles	Same family	No GCSF	Alive after 8 y F/U
27	[4]	2015	Arab	c.758G>A	Arg253His	2	M	ASD	bilateral undescended testis, bilateral inguinal hernia, vesicoureteral reflux, developmental delay	Same family as above	No GCSF	Alive after 5 months
28	[4]	2015	Arab	c.758G>A	Arg253His	36	F	NA	NA	Same family as below	GCSF	Alive after 17 y F/U
29	[4]	2015	Arab	c.758G>A	Arg253His	2	M	NA	NA	Same family as above	GCSF	Alive after 14 y F/U
30	[4]	2015	Arab	c.758G>A	Arg253His	29	M	Pulmonic stenosis	pulmonary hypertension, undescended testes, inguinal hernia, developmental delay		GCSF	Alive after 5 y F/U
31	[4]	2015	Arab	c.765-766delAG		3	F	PFO	dysplastic kidneys, developmental delay	Same family as below	GCSF HSCT	Failure of GCST therapy, Alive after 2 y F/U
32	[4]	2015	Arab	c.765-766delAG		2	M	VSD	pulmonary hypertension, dysplastic kidneys, micropenis, developmental delay	Same family as above	GCSF	Died with sepsis due to poor compliance
33	[4]	2015	Arab	c.765-766delAG		1	F	NA	NA		GCSF	Alive after 5 y F/U
34	[13]	2014	Palestinian	c. 765_delAG	p.S255fs	New born	M	ASD, minimal TR, mild PH	recurrent respiratory infections, FTT, dysmorphic features, prominent superficial venous pattern upon the trunk and abdomen, hepatosplenomegaly, genital ambiguity, micropenis, undervirilized bifid scrotum		GCSF	Responded to GCSF
35	[14]	2015	Turkish	c.175T>C	p. Trp59Arg	3	F	ASD, PDA	Osteomyelitis, skin abscess, recurrent lung infections and otitis media with candida albicans and klebsiella, chronic diarrhea, growth retardation, dysmorphic facial features, gingivitis, hepatomegaly, cutis laxa, and palmar erythema, prominent superficial venous pattern on chest and abdomen		GCSF	Responded well to GCSF
36	[15]	2014				5m	M	Primary pulmonary hypertension (PPH), ASD	Prominent abdominal veins and bilateral undescended testes, Sea blue histiocytosis		GCSF	responded well to GCSF
37	[16]	2014	Turkish	c.623 T> G	p.Leu208Arg	4M	F	PFO, minimal TR	fever, gingivostomatitis, protracted abdominal pain diarrhea, pulmonary infections, No superficial venous pattern or congenital abnormality	Sibling 1	Pegylated GCSF	Responded well to pegylated GCSF not to GCSF- 12 y F/U
38	[16]	2014	Turkish	c.623 T> G	p.Leu208Arg	1	F	None	frequent fever, gingivitis, diarrhea, poor weight gain, No congenital defect, severe interstitial pneumonia	Sibling 2	Pegylated GCSF	Responded well to pegylated GCSF not to GCSF- 10 M F/U
39	[17]	2013	Turkish	NA	p.Leu154Pro	13Y	F	Mild MR	recurrent infections, and growth and developmental delay, gingivitis, recurrent aphthous stomatitis, suppurative otitis media, upper and lower respiratory infections, urinary tract infections, gastroenteritis, renal and perianal abscesses frontal bossing, depressed nasal bridge with upturned nose and retrognatia prominent superficial venous pattern on neck, chest, and abdomen myelokathexis		G-CSF	Responded well to G-CSF

G-CSF, Granulocyte-colony stimulating factor; MVP, Mitral valve prolapse; HSCT, Hematopoietic stem cell transplantation; ANC, absolute neutrophil count; F/U, Follow-up.

Table 3. Known cardiac defects associated with SCN4 and their concomitant mutations.

Defect	# of patients	% among patients with CHD	Mutations
ASD	52	72.2	c.[249G>A], c.[778G>C], c.[565C>T], c.[218+1G>A], c.[935dupT], c.[535+1G>A], c.[758G>A], c.[765-766delAG], c.[175T>C], c.[482G>A], [565C>T], c.[210delC], c.[348G>A], c.[208insC], c.[131C>T], c.[829C>T], c.[766_777del], c.[416G>T], c.[257delA], c.[190_210del] c.[779G>A], c.[554T>C], c.[353>G], c.[347T>C], c.[346A>G]
PDA	8	11.1	c.[249G>A], c.[935dupT], c.[175T>C], c.[778G>C], c.[758G>A]
PH	8	11.1	c.[778G>C], c.[765-766delAG]
MR	6	8.3	c.[394C>T], c.[326–1G>A], c.[766_777del], c.[778G>C], c.[758G>A], c.[461T>C], c.[347T>C]
TR	5	6.9	c.[778G>C], c.[765-766delAG], c.[623T>G], c.[347T>C]
PFO	5	6.9	c.[758G>A], c.[765-766delAG], c.[623T>G], c.[778G>C]
AI	6	8.3	c. [249G > A], c. [829C > T], c. [481C > T], c. [778G > C], c. [482G > A]; [565C > T]
MVP	2	2.8	c.[373_375delAAT]
VSD	1	1.4	NA
PS	2	2.8	NA
WPW	1	1.4	NA
Cor triatrum	1	1.4	NA
Hypoplastic LV	1	1.4	NA
PAPVC	1 (this case)	1.4	NA
No defect	20	-	c.[130C>T], c.[680_684delinsT], c.[758G>A], c.[565C>T], c.[141C>G], c.[623T>G], c.[757C>T], c.[1000_1001del], c.[677+1G>A], c.[829C>T], c.[144C>A], c.[758G>A], c.[347T>C]

Conflict of Interests

There is no conflict of interest

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