

CARDIOVASCULAR SYNDROMES WITH PRIMARY IMMUNODEFICIENCY

MANIFESTĂRI CARDIOVASCULARE ÎN IMUNODEFICIENȚELE PRIMARE

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Summary

The medical community generally identified a rising amount of patients with primary immune deficiency (PID) and cardiovascular system (CVS) comorbidities last year. These CVS malformations might be explained by infectious or autoimmune etiologies, genetic aspects, and the immune system participating in the CVS tissue development. Here, we describe combinations of immune and CVS defects from comprehensive literature.

In addition to some famous combinations of PID with CVS abnormalities, such as DiGeorge syndrome and CHARGE anomaly, here are described CHD in combination with Omenn syndrome, DNA repair defects, common variable immunodeficiency, Roifman syndrome, and others. Moreover, we describe the vascular anomalies in chronic mucocutaneous candidiasis, chronic granulomatous disease, and Wiskott–Aldrich syndrome.

In conclusion, the expanding range of PID needs advanced attention to the potential CVS involvement as an essential benefactor in diagnosing and managing the disease.

Introduction

Primary immunodeficiency diseases encompass a broad spectrum of inheritable disorders commonly associated with susceptibility to infections, malignancies, and immune dysregulation. Therefore, early recognition and correction of immune deficiency are essential. Patients with serious T-cell immune deficiency, such as severe combined immunodeficiency (SCID), should be treated by allogeneic hematopoietic stem cell transplantation or autologous gene therapy. In contrast, antibody deficiency can be corrected by immunoglobulin replacement. The critical role of the immune system in the functioning of numerous organs and systems, as well as the effects of genetic implication, contributes to the multisystem abnormalities often observed in patients with PID.

Additionally, the nonimmune abnormalities can be a clue to establishing the specific etiology of the PID, anticipating potential complications, or choosing the best treatment options. Indeed, nonimmune neurological, bone, gastrointestinal, skin, and endocrine abnormalities are often associated with PIDs, such as purine nucleoside phosphorylase deficiency, adenosine deaminase deficiency, cartilage–hair hypoplasia, ectodermal dysplasia, etc. In recent years, particularly with the significant increase in PID for which molecular defects are identified, many PID conditions are associated with CVS abnormalities.

Here we provide a comprehensive review of PID associated with CVS defects. The review was performed using the PubMed database. The International Union of Immunological Societies Expert Committee for Primary Immunodeficiency classification system was used for searching articles reporting PID associated with cardiac or vascular malformations. Additional associations were identified through an open PubMed search by combining terms such as “primary immunodeficiency” and “cardiac,” “heart,” or “vascular.”

The review is intended for both cardiologists and immunologists. Therefore, following a brief description of the clinical features, the immunological and CVS abnormalities are provided.

Predominantly T lineage defects

Omenn syndrome

Description: Omenn syndrome (OMIM# 603554) was described by the first time by Gilbert Omenn in a child of consanguineous parents [1]. It is characterized by generalized severe erythroderma, lymphadenopathy, eosinophilia, hepatosplenomegaly, failure to thrive, diarrhea, and alopecia [2].

CVS abnormalities: Cardiac manifestations of Omenn syndrome have rarely been described. An infant with Omenn syndrome was found to have biventricular hypertrophy, low FE VS, and severe sinus bradycardia, possibly secondary to eosinophilic endomyocardial disease caused [3]. Another case of a 3-month-old girl with Omenn syndrome was described with right ventricular thrombosis. An echocardiographic study revealed a round structure that filled the apex and corpus of the right ventricle, which is an uncommon finding in Omenn syndrome [4]. An infant was admitted to the hospital at 25 days of life with an initial diagnosis of congenital ichthyosis, then diagnosed with Omenn syndrome did not perform bone marrow examination because of a short episode of cardiac arrest during a biopsy procedure with effective reanimation procedures [2].

Calcium channel deficiency

Description: ORAI-1 deficiency (OMIM# 610277) is an autosomal recessive form of SCID characterized by recurrent infections in infancy, congenital muscular hypotonia, developmental delay, and failure to thrive [5].

CVS abnormalities: CVS abnormalities have not been described in ORAI-1 deficient patients; however, it was demonstrated that inactivation of the highly conserved zebrafish orthologue of ORAI1 resulted in severe heart failure, reduced

ventricular systolic function, bradycardia, and skeletal muscle weakness [6]. Another study's results reveal a critical role of ORA1 in fine-tuning cardiac remodeling. They indicate an inverse mode of action between early developmental stages and disease progression in adulthood, as it operates as a crucial mediator for the hypertrophic response in embryonic myocytes but as a limiting determinant in hypertrophy and fibrosis in neurohumoral evoked cardiac pathology in adults [7].

Chronic mucocutaneous candidiasis

Description: Chronic mucocutaneous candidiasis is a group of diseases represented by recurrent *Candida* infections of the skin, nails, and mucous membranes, which may occur in infancy or later and are frequently accompanied by autoimmune endocrine anomalies (hypoparathyroidism and adrenal insufficiency) [8].

CVS abnormalities: Grouhi et al. described a brain biopsy in one patient that demonstrated periarterial mononuclear cell infiltrates, which is suggestive of endarteritis, and another two patients with chronic mucocutaneous candidiasis with cerebral vasculitis and severe neurologic sequelae [9].

STK-4 deficiency

Description: Autosomal recessive mutations in STK4, known as MST1 (OMIM# 614868), were found among some consanguineous families with frequent bacterial and viral infections, mucocutaneous candidiasis, cutaneous warts, and skin abscesses and congenital heart disease (CHD) [10].

CVS abnormalities: According to Heallen, STK4 is activated by Rassf1A in the heart, promoting apoptosis in cardiac cells and inhibiting cardiac fibroblast proliferation, thus controlling cardiac remodeling and mutations in other murine genes in the STK4/Hippo pathway, also lead to heart defects [11]. Routine echocardiography of 3 patients in Abdollahpour's study identified structural cardiac abnormalities, including atrial septal defect type II, patent foramen ovale, and patent foramen ovale associated with mitral, tricuspid, and pulmonary insufficiency [10]. Sherkat et al.

reported an extraordinary case of primary cardiac T-cell lymphoma and atrial septal defect in an 11-year-old girl with STK4 deficiency, a typical non-Hodgkin type involving just the heart or pericardium without confirmation of extracardiac involvement. The echocardiogram showed a large tumor mass on the right ventricular outflow tract (RVOT). Unfortunately, removing it was impossible, so a Glenn shunt was inserted for RVOT obstruction compensation [12].

DNA repair defects

Ataxia–telangiectasia

Description: Ataxia–telangiectasia is a well-described autosomal recessive disorder characterized by cerebellar ataxia, telangiectasia, oculomotor apraxia, and increased susceptibility to ionizing radiation, predisposition to cancer, insulin resistance, immune deficiency, and premature aging (OMIM# 208900) [13]. Recent studies have provided insight into the dynamic role ATM plays in cardiac remodeling following insults such as β -AR stimulation and MI, indicating that ATM modulates cardiac remodeling by affecting inflammatory response, apoptosis, fibrosis, and hypertrophy in the heart [13].

CVS abnormalities: Bastianon reported a case of ataxia–telangiectasia with mitral valve prolapse, mitral regurgitation, and tricuspid regurgitation [14]. Also, carriers of mutations in a single allele AT-mutated kinase are more exposed to ischemic heart disease [15].

Nijmegen breakage syndrome

Description: Nijmegen breakage syndrome (OMIM# 251260) is a rare AR-genetic disorder caused by mutations within nibrin, a DNA damage repair protein. Hallmarks of Nijmegen breakage syndrome include chromosomal instability and clinical manifestations such as growth retardation, immunodeficiency, and progressive microcephaly [16].

CVS abnormalities: Cernakova et al. reported a case of a newborn with hypotrophy and somatic stigmatization: microcephaly, facial dysmorphism, foramen ovale apertum, and Nijmegen breakage syndrome [17].

Predominantly antibody deficiencies

Common variable immunodeficiency

Description: Common variable immunodeficiency disorder (CVID) is diverse in its clinical presentation and the kinds of deficiency. It is a primary humoral immunodeficiency disorder characterized by decreased serum levels of IgG, IgA, and IgM, frequent sinopulmonary infections, autoimmune disorders, granulomatous diseases, improved risk of malignancy, and impaired antibody response despite the adequate number of B cells [18].

CVS abnormalities: In the Cambray-Gutiérrez's study in adults, 17 patients presented with mitral insufficiency and 2 had aortic insufficiency, 24 - tricuspid insufficiency, up to 12 - pulmonary valve insufficiency, and 8 - pulmonary arterial hypertension [19]. In another clinical case reported by Tsai, CVID is associated with systemic infections, autoimmune diseases, and perpetuated atrial fibrillation [20]. Iranian PID Registry reported 5 CVID patients with a medical history of acute pericarditis from 337 CVID-registered patients [21].

Predominantly defects of neutrophils/macrophages number and function

Barth syndrome

Description: Barth syndrome (OMIM# 302060) is an X-linked autosomal recessive disease characterized by cardiomyopathy, skeletal myopathy, neutropenia, growth retardation, and 3-methylglutaconic aciduria. Barth syndrome (BTHS) patients have a high mortality rate throughout infancy, primarily related to progressive cardiomyopathy and a severely weakened immune system [22].

CVS abnormalities: According to the report from the Barth Syndrome Registry in 2012, 70% of BTHS patients were recognized as having cardiomyopathy in the first year of life, and 12% required cardiac transplantation [23]. The most common cardiomyopathy presented in BTHS is dilated cardiomyopathy (DCM), characterized by the weakening of the heart muscle and enlarged ventricles [24], [25]. Additionally, BTHS patients sometimes present left ventricular noncompaction and less frequently have hypertrophic and restrictive cardiomyopathy [24], [26]. Other cardiac issues include arrhythmia, prolonged corrected QT interval, endocardial fibroelastosis, sudden cardiac arrest, and fetal cardiomyopathy with or without intrauterine fetal demise [24].

Cohen syndrome

Description: Cohen syndrome (OMIM# 216550) is an autosomal recessive disorder initially described as a syndrome including obesity, hypotonia, mental deficiency, and facial, oral, ocular, and limb anomalies. Leukopenia, especially neutropenia, was later described as a feature of Cohen syndrome [27].

CVS abnormalities: Heart defects reported in Cohen syndrome include decreased left ventricular function with age, valvular defects (such as a floppy mitral valve and mitral regurgitation), vascular defects including a dilated descending aorta, cardiac systolic murmurs, ST segment abnormalities (ST-segment depression, T-wave inversion), essential hypertension, and pulmonary hypertension [28]–[33]. Patients also tend to have decreased high-density lipoprotein levels and often meet several criteria for metabolic syndrome [34].

Shwachman–Diamond syndrome

Description: Shwachman–Diamond syndrome (SDS) is an autosomal recessive disorder (OMIM# 260400) described with neutropenia, severe exocrine pancreatic insufficiency, liver abnormalities, and bone marrow failure or myelodysplastic syndrome [35]. The earliest clinical manifestation of the disease usually occurs in infancy as pancytopenia, with the majority being neutropenic, which makes patients

susceptible to infections, malabsorption, leukemia, failure to thrive, and rib cage abnormalities. Other rare associations are cardiac pathology and severe hepatic dysfunction, although mild hepatomegaly and elevated transaminases have also been reported in the literature [36], [37].

CVS abnormalities: Cardiac involvement in SDS is not well documented. However, some fatal cases have been recorded in literature [38], [39]. A retrospective and prospective study carried out by Ryan et al. on 17 cases, which were first analyzed retrospectively based on their data and then followed up for some time to document their cardiac changes using echocardiographic measures, showed that there was abnormal systolic dysfunction in 33% of these patients [40]. Atrioventricular septal defect involvement has also been reported in patients with SDS [41]. A study by Toiviainen-Salo on myocardial function in SDS patients established that no abnormalities were found in the myocardial structure and the cardiac anatomy of these patients. However, they observed alterations in the right ventricular diastolic function at rest and a decreased left ventricular contractility during exercise [42]. All this evidence shows cardiac involvement in SDS, and clinicians should closely monitor such patients as this can lead to dire complications.

WHIM syndrome

Description: (WHIM) syndrome is an autosomal dominant rare combined primary immunodeficiency disorder named by an acronym for the diagnostic tetrad of Warts, Hypogammaglobulinemia, Infections, and Myelokathexis, that is characterized by difficult-to-treat warts, low IgG levels, recurrent bacterial infections, and neutropenia [43].

CVS abnormalities: Severe cardiac conotruncal malformations (Tetralogy of Fallot and double aortic arch) were present in 2 different reports from unrelated pedigrees with other CXCR4 mutations [44], [45].

Well-defined syndromes with immunodeficiency

DiGeorge syndrome

Description: DiGeorge syndrome (DGS, OMIM# 188400) or 22q11.2 deletion syndrome (DS 22q11.2) is a rare condition caused by the q11.2 region missing in chromosome 22. It affects one in 4000 live newborns. Among the clinical presentations of this syndrome are anomalies in the parathyroid glands, the palate, the heart, and the thymus. Therefore, it is also called velocardiofacial syndrome or DiGeorge syndrome. Features commonly identified among patients with 22q11.2 microdeletion include ophthalmologic and renal abnormalities, developmental delay, learning disabilities, schizophrenia, and bipolar disorders, as well as skeletal defects (palate abnormalities or short stature). In addition, patients also have typical dysmorphic facial features, including micrognathia, low-set ears, telecanthus with short palpebral fissures, and upward or downward-slanting eyes with short philtrum and small mouth [46].

CVS abnormalities: It is well known that the most common cardiac defects seen in patients with 22q11.2DS are conotruncal defects, including tetralogy of Fallot, pulmonary atresia with ventricular septal defect, interrupted aortic arch, mainly type B, truncus arteriosus, and conoventricular VSD [47]. Other cardiovascular anomalies have been reported in patients with 22q11.2DS, including hypoplastic left heart syndrome, transposition of great arteries, double outlet right ventricle, total anomalous pulmonary venous connection, atrial septal defect, tricuspid atresia, pulmonary valve stenosis, bicuspid aortic valve or aortic valve stenosis [48]. In Butensky's study, which included 85 patients with DGS, of which 5 (7.4%) had an aortic arch anomaly (3 of them with evidence of aortic root dilation), only one (2.2%) was found to have CHD (isolated bicuspid aortic valve without stenosis) [49].

CHARGE syndrome

Description: CHARGE syndrome (OMIM# 214800) is characterized by a pattern of congenital anomalies (Coloboma of the eye, Heart defects, atresia of the choanae, Retardation of growth, Genital abnormalities, and Ear abnormalities). De novo

mutations of chromodomain helicase DNA binding protein 7 (CHD7) are the primary cause of CHARGE syndrome. The clinical phenotype is highly variable, including a wide spectrum of congenital heart defects.

CVS abnormalities: The spectrum of congenital heart disease is highly variable in CHARGE syndrome and encompasses mild cardiac malformations that may not require intervention to more severe malformations that require cardiothoracic surgery in infancy. Conotruncal defects (31–42%) and atrioventricular septal defects (13–17%) with associated or isolated PDA and aortic arch abnormalities are seen more frequently in individuals with CHARGE than the entire population of patients with congenital heart disease [48]. The most extensive study of individuals with CHARGE syndrome examining the spectrum of congenital heart defects included 299 individuals with CHARGE syndrome and demonstrates the over-representation of conotruncal defects and ASD/VSDs [50].

Roifman syndrome

Description: Roifman syndrome (OMIM# 300258) is characterized by antibody deficiency, spondyloepiphyseal dysplasia, growth retardation, retinal dystrophy and associated manifestations that include intellectual disability, dysmorphic features, and hypogonadism [50].

CVS abnormalities: An adolescent boy with Roifman Syndrome was reported with left ventricular noncompaction and heart failure [51].

Conclusion

In conclusion, the large spectrum of PID requires increased alertness to the possibility of CVS involvement as an essential contributor to the prognostic and management of these patients.

Bibliography

1. Omenn GS. Familial Reticuloendotheliosis With Eosinophilia. *N Engl J Med*. 1965 Aug 19;273:427-32. doi: 10.1056/NEJM196508192730806. PMID: 14328107.
2. Szaflarska A, Noworolska APD, Kowalczyk D, Zembala M, van der Burg M, van Dongen JJM. Omenn's syndrome in cousins: different clinical course and identical RAG1 mutation. *Pediatrics Polska*. (2009). 84:367–72. doi: 10.1016/S0031-3939(09)70126-X
3. Brückmann C, Lindner W, Roos R, Permanetter W, Haas RJ, Haworth SG, Belohradsky BH. Severe pulmonary vascular occlusive disease following bone marrow transplantation in Omenn syndrome. *Eur J Pediatr*. 1991 Feb;150(4):242-5. doi: 10.1007/BF01955521. PMID: 2029913.
4. Kilic SS, Cil E, Meral A, Villa A. Cardiac thrombus in Omenn syndrome. *Pediatr Cardiol*. 2005 Sep-Oct;26(5):694-7. doi: 10.1007/s00246-005-0868-9. PMID: 16088419.
5. McCarl CA, Picard C, Khalil S, Kawasaki T, Röther J, Papolos A, Kutok J, Hivroz C, Ledest F, Plogmann K, Ehl S, Notheis G, Albert MH, Belohradsky BH, Kirschner J, Rao A, Fischer A, Feske S. ORAI1 deficiency and lack of store-operated Ca²⁺ entry cause immunodeficiency, myopathy, and ectodermal dysplasia. *J Allergy Clin Immunol*. 2009 Dec;124(6):1311-1318.e7. doi: 10.1016/j.jaci.2009.10.007. PMID: 20004786; PMCID: PMC2829767.
6. Völkers, M., Dolatabadi, N., Gude, N., Most, P., Sussman, M. A., & Hassel, D. (2012). Orail deficiency leads to heart failure and skeletal myopathy in zebrafish. *Journal of Cell Science*, 125(2), 287-294. <https://doi.org/10.1242/jcs.090464>
7. Segin, S., Berlin, M., Richter, C., Medert, R., Flockerzi, V., Worley, P., Freichel, M., & Camacho Londoño, J. E. (2020). Cardiomyocyte-Specific Deletion of Orail Reveals Its Protective Role in Angiotensin-II-Induced Pathological Cardiac Remodeling. *Cells*, 9(5). <https://doi.org/10.3390/cells9051092>
8. Liu L, Okada S, Kong XF et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. *J Exp Med*. 2011 Aug 1;208(8):1635-48. doi: 10.1084/jem.20110958. Epub 2011 Jul 4. PMID: 21727188; PMCID: PMC3149226.
9. Grouhi M, Dalal I, Nisbet-Brown E, Roifman CM. Cerebral vasculitis associated with chronic mucocutaneous candidiasis. *J Pediatr*. 1998 Oct;133(4):571-4. doi: 10.1016/s0022-3476(98)70072-1. PMID: 9787702.
10. Abdollahpour H, Appaswamy G, Kotlarz D, et al. The phenotype of human STK4 deficiency. *Blood*. 2012 Apr 12;119(15):3450-7. doi: 10.1182/blood-2011-09-378158. Epub 2012 Jan 31. PMID: 22294732; PMCID: PMC3325036.

11. Heallen T, Zhang M, Wang J, et al. Hippo pathway inhibits Wnt signaling to restrain cardiomyocyte proliferation and heart size. *Science*. 2011 Apr 22;332(6028):458-61. doi: 10.1126/science.1199010. PMID: 21512031; PMCID: PMC3133743.
12. Sherkat R, Sabri MR, Dehghan B, et al. EBV lymphoproliferative-associated disease and primary cardiac T-cell lymphoma in a STK4 deficient patient: A case report. *Medicine (Baltimore)*. 2017 Dec;96(48):e8852. doi: 10.1097/MD.0000000000008852. PMID: 29310365; PMCID: PMC5728766.
13. Thrasher P, Singh M, Singh K. Ataxia-Telangiectasia Mutated Kinase: Role in Myocardial Remodeling. *J Rare Dis Res Treat*. 2017;2(1):32-37. Epub 2016 Dec 16. PMID: 29152614; PMCID: PMC5690556.
14. BASTIANON V, GIGLIONI E, BUSINCO L, et al. Cardiac Anomalies in Ataxia-Telangiectasia. *Am J Dis Child*. 1993;147(1):20-21. doi:10.1001/archpedi.1993.02160250022008
15. Su Y, Swift M. Mortality rates among carriers of ataxia-telangiectasia mutant alleles. *Ann Intern Med*. 2000 Nov 21;133(10):770-8. doi: 10.7326/0003-4819-133-10-200011210-00009. PMID: 11085839.
16. Martins S, Erichsen L, Datsi A, Wruck W, Goering W, Chatzantonaki E, de Amorim VCM, Rossi A, Chrzanowska KH, Adjaye J. Impaired p53-Mediated DNA Damage Response Contributes to Microcephaly in Nijmegen Breakage Syndrome Patient-Derived Cerebral Organoids. *Cells*. 2022 Feb 25;11(5):802. doi: 10.3390/cells11050802. PMID: 35269426; PMCID: PMC8909307.
17. Cernakova I, Kvasnicova M, Lovasova Z, Badova N, Drabek J, Bouchalova K, Trojanec R, Hajdich M. A duplication dup(4)(q28q35.2) de novo in a newborn. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2006 Jul;150(1):113-6. doi: 10.5507/bp.2006.016. PMID: 16936912.
18. Pescador Ruschel MA, Vaqar S. Common Variable Immunodeficiency. 2022 Jul 4. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. PMID: 31747194.
19. Cambray-Gutiérrez JC, Fernández-Muñoz MJ, Del Rivero-Hernández LG, López-Pérez P, Chávez-García AA, Segura-Méndez NH. Cardiopatías estructurales y funcionales en pacientes adultos con inmunodeficiencia común variable [Structural and functional heart diseases in adult patients with common variable immunodeficiency]. *Rev Alerg Mex*. 2015 Apr-Jun;62(2):91-7. Spanish. PMID: 25958371.
20. Tsai, J., Nguyen, N.H. and Dylewski, J.R. (2020), The Correlation between Common Variable Immunodeficiency and Atrial Fibrillation: Cardiac Implantable Electronic Devices-associated infection by *Stenotrophomonas maltophilia*: A case report. *The FASEB Journal*, 34: 1-1. <https://doi.org/10.1096/fasebj.2020.34.s1.06870>

21. Ramzi N, Yazdani S, Talakoob H, Jamee M, Karim H, Azizi G. Acute pericarditis: A peculiar manifestation of common variable immune deficiency. *Allergol Immunopathol (Madr)*. 2021 May 1;49(3):115-119. doi: 10.15586/aei.v49i3.99. PMID: 33938196.
22. Jan Dudek, Christoph Maack, Barth syndrome cardiomyopathy, *Cardiovascular Research*, Volume 113, Issue 4, 15 March 2017, Pages 399–410, <https://doi.org/10.1093/cvr/cvx014>
23. Roberts AE, Nixon C, Steward CG, Gauvreau K, Maisenbacher M, Fletcher M, Geva J, Byrne BJ, Spencer CT. The Barth Syndrome Registry: distinguishing disease characteristics and growth data from a longitudinal study. *Am J Med Genet A*. 2012 Nov;158A(11):2726-32. doi: 10.1002/ajmg.a.35609. Epub 2012 Oct 8. PMID: 23045169.
24. Clarke, S.L., Bowron, A., Gonzalez, I.L. et al. Barth syndrome. *Orphanet J Rare Dis* 8, 23 (2013). <https://doi.org/10.1186/1750-1172-8-23>
25. Pang J, Bao Y, Mitchell-Silbaugh K, Veevers J, Fang X. Barth Syndrome Cardiomyopathy: An Update. *Genes (Basel)*. 2022 Apr 8;13(4):656. doi: 10.3390/genes13040656. PMID: 35456462; PMCID: PMC9030331.
26. Taylor C, Rao ES, Pierre G, Chronopoulou E, Hornby B, Heyman A, Vernon HJ. Clinical presentation and natural history of Barth Syndrome: An overview. *J Inherit Metab Dis*. 2022 Jan;45(1):7-16. doi: 10.1002/jimd.12422. Epub 2021 Aug 15. PMID: 34355402.
27. Rodrigues JM, Fernandes HD, Caruthers C, Braddock SR, Knutsen AP. Cohen Syndrome: Review of the Literature. *Cureus*. 2018 Sep 18;10(9):e3330. doi: 10.7759/cureus.3330. PMID: 30473963; PMCID: PMC6248805.
28. Kivitie-Kallio S, Eronen M, Lipsanen-Nyman M, Marttinen E, Norio R. Cohen syndrome: evaluation of its cardiac, endocrine and radiological features. *Clin Genet*. 1999 Jul;56(1):41-50. doi: 10.1034/j.1399-0004.1999.560106.x. PMID: 10466416.
29. Kivitie-Kallio S, Eronen M, Lipsanen-Nyman M, Marttinen E, Norio R. Cohen syndrome: evaluation of its cardiac, endocrine and radiological features. *Clin Genet*. 1999 Jul;56(1):41-50. doi: 10.1034/j.1399-0004.1999.560106.x. PMID: 10466416.
30. Schlichtemeier TL, Tomlinson GE, Kamen BA, Waber LJ, Wilson GN. Multiple coagulation defects and the Cohen syndrome. *Clin Genet*. 1994 Apr;45(4):212-6. doi: 10.1111/j.1399-0004.1994.tb04026.x. PMID: 8062442.
31. Kivitie-Kallio S, Norio R. Cohen syndrome: essential features, natural history, and heterogeneity. *Am J Med Genet*. 2001 Aug 1;102(2):125-35. doi: 10.1002/1096-8628(20010801)102:2<125::aid-ajmg1439>3.0.co;2-0. PMID: 11477603.
32. Sack J, Friedman E. Cardiac involvement in the Cohen syndrome: a case report. *Clin Genet*. 1980 May;17(5):317-9. doi: 10.1111/j.1399-0004.1980.tb00156.x. PMID: 7438489.

33. Cokkinos P, Gkouziouta A, Karavolias G, Kariofillis P, Voudris V. Idiopathic pulmonary arterial hypertension in a young patient with the Cohen syndrome. *Hellenic J Cardiol*. 2013 Mar-Apr;54(2):143-6. PMID: 23557616.
34. Limoge F, Faivre L, Gautier T, Petit JM, Gautier E, Masson D, Jegou G, El Chehadeh-Djebbar S, Marle N, Carmignac V, Deckert V, Brindisi MC, Edery P, Ghoumid J, Blair E, Lagrost L, Thauvin-Robinet C, Duplomb L. Insulin response dysregulation explains abnormal fat storage and increased risk of diabetes mellitus type 2 in Cohen Syndrome. *Hum Mol Genet*. 2015 Dec 1;24(23):6603-13. doi: 10.1093/hmg/ddv366. Epub 2015 Sep 10. PMID: 26358774.
35. Lawal OS, Mathur N, Eapi S, Chowdhury R, Malik BH. Liver and Cardiac Involvement in Shwachman-Diamond Syndrome: A Literature Review. *Cureus*. 2020 Jan 16;12(1):e6676. doi: 10.7759/cureus.6676. PMID: 32104616; PMCID: PMC7026866.
36. Ryan TD, Jefferies JL, Chin C, Sticka JJ, Taylor MD, Harris R, Moore J, Goodridge E, Mount L, Bolyard AA, Otto B, Jones A, Shimamura A, Davies S, Myers K. Abnormal circumferential strain measured by echocardiography is present in patients with Shwachman-Diamond syndrome despite normal shortening fraction. *Pediatr Blood Cancer*. 2015 Jul;62(7):1228-31. doi: 10.1002/pbc.25456. Epub 2015 Mar 2. PMID: 25732529; PMCID: PMC4819242.
37. Revert Lazaro F, Perez Monjardin E, Perez AP 2006 [Hypertransaminasemia as a manifestation of Shwachman-Diamond syndrome]. *An Pediatr (Barc)* 64: 481–484
38. Savilahti E, Rapola J. Frequent myocardial lesions in Shwachman's syndrome. Eight fatal cases among 16 Finnish patients. *Acta Paediatr Scand*. 1984 Sep;73(5):642-51. doi: 10.1111/j.1651-2227.1984.tb09989.x. PMID: 6485783.
39. Kopel L, Gutierrez PS, Lage SG. Dilated cardiomyopathy in a case of Shwachman-Diamond syndrome. *Cardiol Young*. 2011 Oct;21(5):588-90. doi: 10.1017/S1047951111000308. Epub 2011 Apr 13. PMID: 21486516.
40. Kopel L, Gutierrez PS, Lage SG. Dilated cardiomyopathy in a case of Shwachman-Diamond syndrome. *Cardiol Young*. 2011 Oct;21(5):588-90. doi: 10.1017/S1047951111000308. Epub 2011 Apr 13. PMID: 21486516.
41. Le Gloan L, Blin N, Langlard JM. Atrioventricular septal defect in a case of Shwachman-Diamond syndrome. *Cardiol Young*. 2014 Jun;24(3):549-51. doi: 10.1017/S104795111300084X. Epub 2013 Jun 27. PMID: 23803361.
42. Toiviainen-Salo S, Pitkänen O, Holmström M, Koikkalainen J, Lötjönen J, Lauerma K, Taskinen M, Savilahti E, Smallhorn J, Mäkitie O, Kivistö S. Myocardial function in patients with Shwachman-Diamond syndrome: aspects to consider before stem cell transplantation. *Pediatr Blood Cancer*. 2008 Oct;51(4):461-7. doi: 10.1002/pbc.21686. PMID: 18646182.
43. Heusinkveld LE, Majumdar S, Gao JL, McDermott DH, Murphy PM. WHIM Syndrome: from Pathogenesis Towards Personalized Medicine and Cure. *J Clin Immunol*.

2019 Aug;39(6):532-556. doi: 10.1007/s10875-019-00665-w. Epub 2019 Jul 16. PMID: 31313072; PMCID: PMC6698215.

44. Beaussant Cohen S, Fenneteau O, Plouvier E, Rohrlich PS, Daltroff G, Plantier I, Dupuy A, Kerob D, Beaupain B, Bordigoni P, Fouyssac F, Delezoide AL, Devouassoux G, Nicolas JF, Bensaid P, Bertrand Y, Balabanian K, Chantelot CB, Bachelier F, Donadiou J. Description and outcome of a cohort of 8 patients with WHIM syndrome from the French Severe Chronic Neutropenia Registry. *Orphanet J Rare Dis.* 2012 Sep 25;7:71. doi: 10.1186/1750-1172-7-71. PMID: 23009155; PMCID: PMC3585856.

45. Badolato R, Dotta L, Tassone L, Amendola G, Porta F, Locatelli F, Notarangelo LD, Bertrand Y, Bachelier F, Donadiou J. Tetralogy of fallot is an uncommon manifestation of warts, hypogammaglobulinemia, infections, and myelokathexis syndrome. *J Pediatr.* 2012 Oct;161(4):763-5. doi: 10.1016/j.jpeds.2012.05.058. Epub 2012 Jun 27. PMID: 22748845; PMCID: PMC3458406.

46. Cortés-Martín J, Peñuela NL, Sánchez-García JC, Montiel-Troya M, Díaz-Rodríguez L, Rodríguez-Blanco R. Deletion Syndrome 22q11.2: A Systematic Review. *Children (Basel).* 2022 Aug 3;9(8):1168. doi: 10.3390/children9081168. PMID: 36010058; PMCID: PMC9406687.

47. Unolt M, Versacci P, Anaclerio S, Lambiase C, Calcagni G, Trezzi M, Carotti A, Crowley TB, Zackai EH, Goldmuntz E, Gaynor JW, Digilio MC, McDonald-McGinn DM, Marino B. Congenital heart diseases and cardiovascular abnormalities in 22q11.2 deletion syndrome: From well-established knowledge to new frontiers. *Am J Med Genet A.* 2018 Oct;176(10):2087-2098. doi: 10.1002/ajmg.a.38662. Epub 2018 Apr 16. PMID: 29663641; PMCID: PMC6497171.

48. Butensky A, de Rinaldis CP, Patel S, Edman S, Bailey A, McGinn DE, Zackai E, Crowley TB, McDonald-McGinn DM, Min J, Goldmuntz E. Cardiac evaluation of patients with 22q11.2 duplication syndrome. *Am J Med Genet A.* 2021 Mar;185(3):753-758. doi: 10.1002/ajmg.a.62032. Epub 2020 Dec 27. PMID: 33369133.

49. Corsten-Janssen N, Kerstjens-Frederikse WS, du Marchie Sarvaas GJ, Baardman ME, Bakker MK, Bergman JE, Hove HD, Heimdal KR, Rustad CF, Hennekam RC, Hofstra RM, Hoefsloot LH, Van Ravenswaaij-Arts CM, Kapusta L. The cardiac phenotype in patients with a CHD7 mutation. *Circ Cardiovasc Genet.* 2013 Jun;6(3):248-54. doi: 10.1161/CIRCGENETICS.113.000054. PMID: 23677905.