New insights on genetic variants and phenotypic features of childhood large-vessel vasculopathy: a systematic review and single-centre series

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Abstract

Objective

To describe the phenotypic, genetic, and outcome characteristics of large-vessel vasculopathy (LVV) in childhood associated with genetic variants. Additionally, a systematic literature review was conducted to delineate the differences between LVV with and without genetic variants.

Methods

The medical records of all children with LVV seen between January 2000 and September 2022 at our institution were retrospectively reviewed for demographic, clinical and genetic data, and outcomes at the last follow-up visit. In addition, we systematically reviewed the literature for the clinical features and known variants of previously reported cases.

Results

Eleven patients with childhood LVV were identified; five (three males) of them had proven genetic variants (two DOCK8 *variants, one* FOXP3*, one DiGeorge syndrome, and one* ZNF469 *variant), while six patients had sporadic childhood LVV. Remarkably, patients with genetic variants were younger and had early-onset disease. However, the diagnosis of LVV was delayed compared to those without genetic variants. All patients with genetic variants were treated with corticosteroids, and three patients required sequential immunosuppressive drugs. Four patients underwent surgical intervention, and one received a haematopoietic stem-cell transplant (HSCT). Three patients achieved clinical remission, and two died. Furthermore, data from 20 previously published cases was extracted from the literature. All patients had inherited disorders. Of those, 14 patients had a genetically proven diagnosis. Most of them are treated with corticosteroids and immunosuppressive drugs, with partial responses. Two patients underwent HSCT. There were four deaths.*

Conclusion

This study demonstrates that a variety of inherited disorders may contribute to childhood LVV. Strong genetic evidence and the preponderance of autosomal-recessive inheritance may allow us to propose that monogenic LVV is a distinct entity.

Key words

large-vessel vasculitis, vasculopathy, aortitis, Takayasu's arteritis, inborn error of immunity, genetic variant

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Introduction

Systemic vasculitis is a heterogeneous group of inflammatory diseases affecting small and large blood vessels with or without necrosis (1, 2). Large-vessel vasculopathy (LVV) rarely affects children. Takayasu's arteritis (TAK) is the most common form of LVV in children. Classically, it affects the aorta and its major branches, with evidence of intramural granulomatous inflammation causing aneurysmal and stenotic changes and a high risk of thrombus formation (3, 4). Eventually, without proper treatment, these changes can result in ischaemia and devastating organ dysfunction (5). The aetiology and pathogenesis of LVV, including TAK, remain incompletely defined. However, like other autoimmune diseases, environmental, infectious, and genetic factors may contribute to its pathophysiology. Notably, the identification of single-gene defects has contributed to a better understanding of the clinical variability and recognition of rare variants of systemic vasculitis. Several reports have described TAK and aortitis in patients with inborn errors of immunity (IEIs). Interestingly, these patients had extensive vasculitis with serious morbidity or death. The most common IEIs associated with aortitis and TAK are Wiskott-Aldrich syndrome (WAS), Blau syndrome, and hyper-IgE syndrome (HIES) (6-9). It is worth mentioning that the International Union of Immunological Societies Expert Committee defines IEI as a group of heterogeneous diseases caused by genetic mutation and manifested by immune deficiency with increased susceptibility to infections, autoimmunity, autoinflammatory diseases, allergy, and/or malignancy (10).

Available data on childhood LVV associated with genetic variants or underlying immune dysregulation is limited to case reports. Given the high prevalence of consanguineous marriage and the high frequency of IEIs in our society, we investigated the phenotypic, genetic, and outcome characteristics of LVV in childhood associated with genetic variants (11, 12). In addition, we sought to distinguish between LVV with and without genetic variations by conducting a thorough assessment of the literature for all previously described cases.

Methods

Study design and cohort data collection

This is a cross-sectional retrospective cohort study that comprised all children with LVV who were followed up at King Faisal Specialist Hospital and Research Centre, Riyadh (KFSRC-R), Saudi Arabia, from January 2000 to September 2022. To ensure that all children with LVV were included, we retrieved our paediatric rheumatology database and coordinated with the medical records department. The included patients were younger than 14 years of age at diagnosis and fulfilled the EULAR/PRINTO/PRES criteria (1). In this study, all genetic variants, including known pathogenic variants and variants of uncertain significance (VUS), or novel variants, were considered even without a functional assay. All enrolled patients' medical records were reviewed for demographic, clinical manifestations, and diagnostic assessment, including autoantibody profiles, imaging, tissue biopsy, and genetic testing, when available. If applicable, information on consanguinity and family history of an autoimmune disease or similar disease, treatment, complications, outcomes, and cause of death were included. The long-term assessment of the disease was completed at the last follow-up visit using the Paediatric Vasculitis Damage Index (PVDI) (13, 14).

Of note, patients with LVV associated with another definite autoimmune disease or patients with insufficient medical data are excluded.

Literature systematic review identified cases

Search strategy. We systematically reviewed the previous reports of childhood LVV with genetic variants. A comprehensive search was performed on PubMed and Google Scholar for relevant studies published up to September 2022. The search was limited to literature written in English and conducted on humans, applying the following MeSH terms: large-vessel vasculi-

tis; Takayasu's arteritis; aortitis; vasculopathy; aortitis syndrome; and terms related to IEIs; genetic diseases, genetic mutation, genetic variant, immune dysregulation, immunodeficiency, autoimmune diseases, and autoinflammatory disorders.

Because of the rarity of these entities, in addition to the observational data, we considered case reports and case series. The articles were first screened based on the title and abstract. All potentially relevant articles were checked, and the full text was assessed. Also, the reference lists of all full-text articles identified in this search were checked for additional appropriate studies. Furthermore, two authors assessed and checked the quality of the literature review process. The articles were evaluated by SA independently using the inclusion criteria, which were then reviewed and clarified by SMA. It was not essential to involve a third reviewer; disagreements were discussed until a consensus was reached. This systematic review was carried out using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 checklist.

Data extraction

The following data were extracted from each selected study: study design, number of patients, age of patients at inclusion, gender, diagnostic criteria used for patient inclusion, duration of follow-up, treatment (excluding non-steroidal anti-inflammatory drugs, glucocorticoids), response to treatment (*i.e.* overall response rate as well as partial and complete response rates), and outcomes, when available.

Statistical considerations

Statistical analyses were performed using the SAS software package, v. 9.4 (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA). Descriptive statistics for continuous variables were reported as median and interquartile range (IQR), and mean ± standard deviation (SD) was used when deemed necessary. Categorical variables were summarised as frequency and percentage.

Ethical considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki (2000). The Ethics Committee of the Research Affairs Council at KFSHRC approved the study protocol under RAC no. 2211228. All clinical and laboratory assessments were the result of routine medical care. Informed consent for genetic testing as part of patient care was obtained from the parents at the time of blood extraction. All collected data was analysed under confidentiality practices, and no personal identity was required.

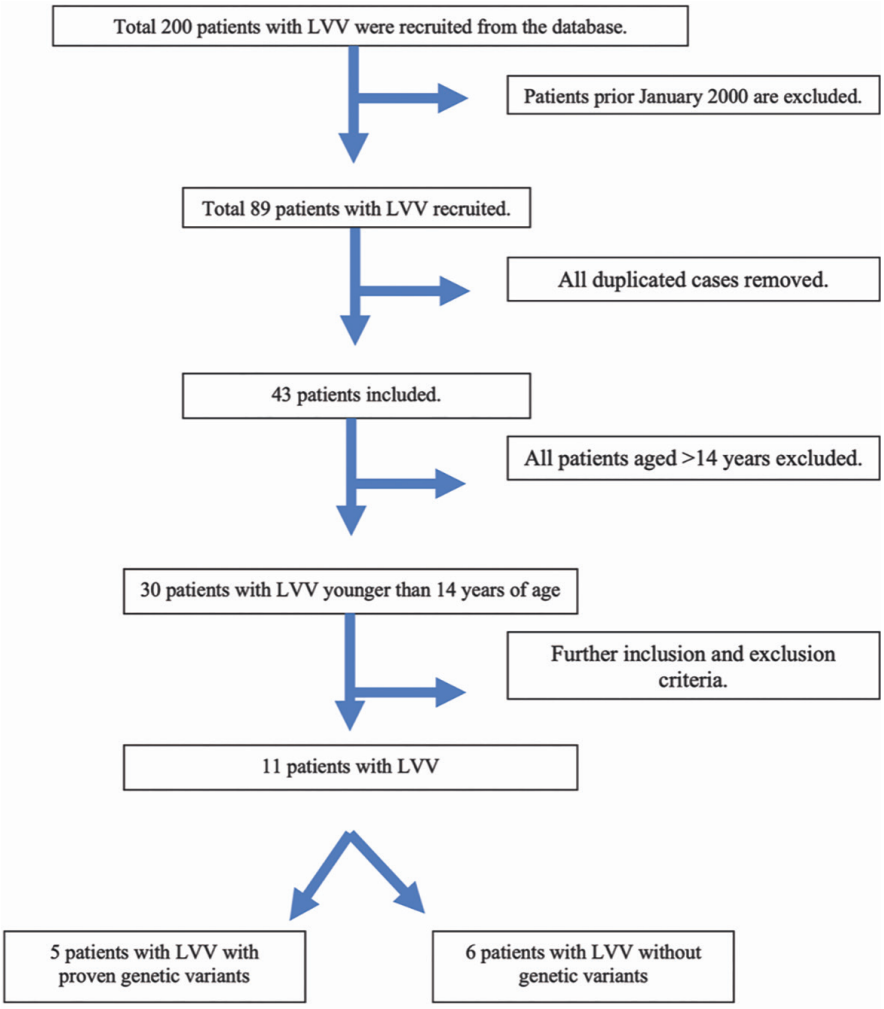

Fig. 1. Flow chart of the KFSHRC LVV cohort.
KFSHRC: King Faisal Specialist Hospital and Research Center; LVV: large vessels vasculopathy.

Results

KFSHRC childhood LVV cohort

Data for 200 patients were retrieved from our KFSHRC database. Only 89 LVV patients met the study criteria. Further patients were excluded, either because they were duplicates or because they did not meet the inclusion criteria. As shown in Figure 1, eleven patients had childhood LVV. Interestingly, five (three males) patients had underlying IEIs proven by molecular genetic studies; all of them were products of consanguineous marriage. In contrast, six (three male) patients had childhood LVV without a clear underlying disease, with only one patient belonging to a consanguineous family. Remarkably, there was a delay in the diagnosis of LVV, with a median age of 12 (IQR 11.0-13.0) years, while the mean time interval between the onset of the underlying disease and the diagnosis of LVV was 10.6 (±3.7) years.

Patients with LVV and genetic variants experienced symptoms before their second birthday. Patients with genetic variants typically present at a younger age. Two patients with recurrent chest infections, skin abscesses, and eczema

Table I. Demographic clinical features and molecular genetics of monogenic large-vessel vasculopathy of KFSHRC cohort.

Diagnosis	Gender	Age at the onset of the primary disease	Age at LVV diagnosis	Vascular findings	ESR/ CRP	Abnormal imaging	Histopathology (Aorta)	Gene	Zygosity	Variant	Treatment	Surgical intervention	Death
HIES	F	Infancy	13 years	Diffuse aneurysmal dilatation of ATO, AO	High	CTA,MRI/ MRA	Lymphoplasmacytic, eosinophilic infiltrate	DOCK8	Het	c.5625 T>G of NM_203447.3	CS, AZA	Yes	No
HIES	M	Infancy	7 years	AA, ATO, AO	High	CTA, MRI/MRA, CA	Eosinophilic infiltration and calcification	DOCK8	Hom	A large deletion	CS	Yes	Yes
IPEX	M	2 years	11 years	AA, ATO AO	High	CTA, MRI/MRA	Not done	FOXP3	Hemizygous	1040 G>A of c.NM_014009.4	CS, MMF TC,	No	Yes
Novel mutation	M	2 years	12 years	AA, ATO	High	CTA, MRI/MRA	Cystic medial (fibromyxoid) degeneration	KDM5B	Hom	ZNF469 variant and de novo variant	CS TC, IF MTX	Yes	No
DiGeorge syndrome	F	1 year	17 years	AA, ATO, AO	High	CTA, MRA		Ch 22q11		Deletion in 22q11	CS, MTX	Yes	No

*All patients are product of consanguineous marriage.
KFSHRC: King Faisal Specialist Hospital and Research Center; HIES: Hyper IgE syndrome; IPEX: immune dysregulation, poly-endocrinopathy, enteropathy and X-linked inherited; F: female; M: male; ATO: ascending thoracic aorta; AO: abdominal aorta; AA: aortic arch; CTA: computed tomography angiography; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; CA: conventional angiography; Het: heterozygous; Hom: homozygous; CS: corticosteroids; AZA: azathioprine; MMF: mycophenolate mofetil; MTX: methotrexate; TC: tocilizumab; IF: infliximab.

proved to have *DOCK8* variants. One patient with the *FOXP3* variant presented with very early-onset inflammatory bowel disease; one patient had DiGeorge syndrome, and one patient had skeletal dysplasia and inflammatory bone disease with a homozygous *ZNF469* variant and a de novo variant in *KDM5B* (Table I). All patients with genetic variants had progressive extensive LVV, affecting mainly the aorta and its branches, which was confirmed by imaging studies. Hypertension, abdominal pain, fever, and vascular bruit were the most frequent clinical features. In addition to the abnormal imaging studies, elevated inflammatory markers, leukocytosis, and a raised hepatic profile were the main laboratory findings. Interestingly, none of the patients had antineutrophil cytoplasmic antibody positivity. However, only two patients had anti-nuclear antibodies with no significant extractable nuclear antigen. All patients had cardiomegaly and evidence of valvular disease proven by echocardiography. Three patients had tissue biopsies; two patients with HIES showed eosinophilic infiltration with chronic inflammation and calcification, while one patient with a homozygous *ZNF469* variant showed marked cystic degeneration, consistent with myxoid changes.

Apart from transaminitis, other variables were comparable between patients with and without genetic variants. Table II compares patients with and without genetic variants for childhood LVV in terms of the frequency of clinical and laboratory findings.

Overall, patients with genetic variants required more treatment. All patients received corticosteroids. However, four patients with genetic variants were treated with conventional disease-modifying anti-rheumatic drugs (cDMARDs), and two of them required biologic agents. Furthermore, four patients underwent surgical intervention, and one patient underwent hematopoietic stem cell transplantation (HSCT). In contrast, six patients without genetic variants were treated with cDMARDs, and only one patient required biological treatment. Two patients underwent surgery. In general, most of the patients achieved clinical remission. However, compared to patients without genetic variants, those with genetic variants had a higher PVDI (5.2±1.7 *vs*. 2.6±1.9). Two deaths occurred among patients with genetic variants, one from a serious infection, and the other was reported to have passed away unexpectedly at home.

Literature identified cases

A total of 72 publications were obtained. The first round of elimination was directly performed based on the screening of titles and abstracts, and 24 articles were excluded because they either had an adult disease onset or had no genetic data. We evaluated 48 potentially relevant articles and downloaded their full texts. Furthermore, 31 articles were excluded (Fig. 2). Cases of LVV without genetic variants or those with LVV associated with other autoimmune diseases, such as systemic lupus erythematosus or infection, were excluded. Finally, only 17 articles with a total of 20 LVV with genetic defects were selected for this analysis (15-29). All the included patients had inherited disorders. Table III summarises the characteristics of the 20 patients, including their genetic features. Fourteen patients had genetically proven diagnoses. It is worth mentioning that the diagnosis in the other six patients was based on the expert physician's opinion, the fulfilment of the diagnostic criteria, and the presence of an index case in the affected family.

Only 14 patients had documented treatment details. Apart from corticosteroids, which were used in 12 patients, cDMARDs were initiated in nine pa-

Table II. Comparison of monogenic and sporadic large-vessel vasculopathy of KFSHRC cohort.

	With gene LVV	Without gene LVV	*p*-value
Age at LVV diagnosis, years, median (IQR)	12 (11-13)	10 (8.3-11.8)	
Consanguinity	5 (100)	1 (16.7)	0.02
Clinical manifestation	no. of patients (%)	no. of patients (%)	
Fever	2 (40)	4 (66.7)	NS
Lymphadenopathy/hepatosplenomegaly	4 (80)	1 (16.7)	0.08
Arthritis/arthralgia	3 (60)	2 (33.3)	NS
Headache	1 (20)	3 (50)	NS
Seizure	1 (20)	2 (33.3)	NS
Abdominal pain	2 (40)	4 (66.7)	NS
Diarrhoea	2 (40)	2 (33.3)	NS
Hypertension	2 (40)	5 (83.3)	NS
Vascular bruit	4 (80)	2 (33.3)	NS
Claudication	2 (40)	3 (50)	NS
Laboratory findings			
High ESR/CRP	5 (100)	6 (100)	NS
Leukocytosis	5 (100)	3 (50)	NS
Abnormal platelets	5 (100)	2 (33.3)	NS
Abnormal renal profile	1 (20)	2 (33.3)	NS
Abnormal urinalysis or PR/CRT ratio	0 (0)	2 (33.3)	NS
ANA (Negative)	3 (60)	5 (83.3)	NS
ANCA (Negative)	5 (100)	4 (66.7)	NS
Abnormal hepatic profile	5 (100)	1 (16.7)	0.02
Radiology			
Abnormal echo	5 (100)	3 (50)	NS
Abnormal CT/MRA angiography	5 (100)	6 (100)	NS
Histopathology findings	3 (60)	0 (0.00)	NS
PVDI (mean, SD)	5.2 (±1.7)	2.6 (±1.9)	0.04

LVV: large-vessel vasculopathy; ESR: erythrocyte sedimentation rate; CRP: C reactive protein: PR/CRT: protein/creatinine ratio; ANA: anti-nuclear antibody; ANCA: antineutrophil cytoplasmic antibody; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; CTA: computed tomography angiography; PVDI: paediatric vasculitis damage index; NS: not statistically significant.

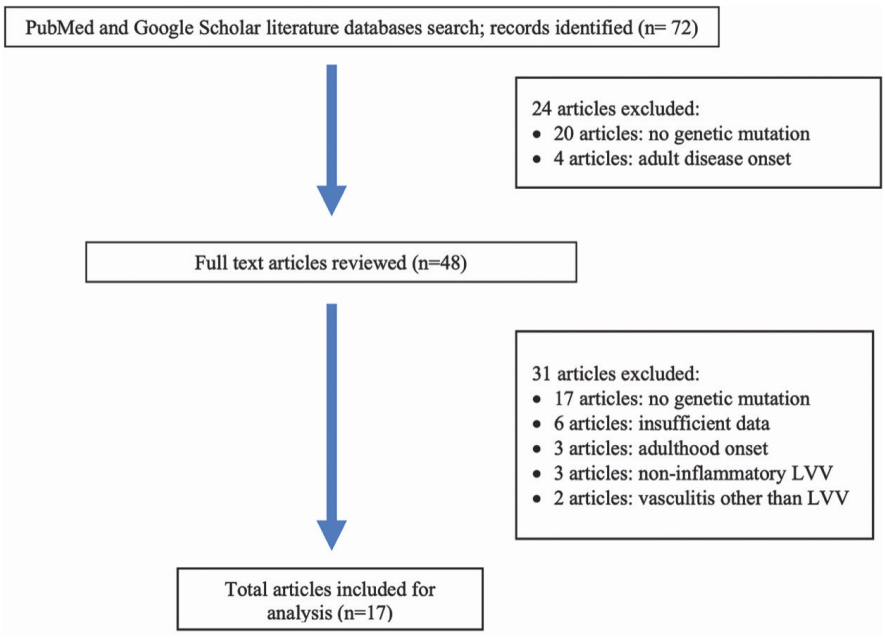

Fig. 2. Flowchart of the literature identified cases for LVV.

tients. Two patients received biologic DMARDs (one patient treated with infliximab and another patient treated with tocilizumab). Furthermore, two patients completed HSCT, and only three patients underwent surgical intervention. Most of the patients showed a reasonable therapeutic response. However, with regards to the long-term outcomes, two patients had neurological complications, and four patients died.

Discussion

The exact aetiopathogenesis of most autoimmune diseases, including systemic vasculitis, remains poorly understood. However, the most plausible theory in this regard is the complex interaction between genetic susceptibility, epigenetics, and environmental factors. Furthermore, immune dysregulation disorders due to genetic defects are gaining more attention as an underlying cause of various autoimmune and autoinflammatory conditions (30-32). There have been several reports of TAK coexisting with other immune-mediated diseases such as optic neuritis, chronic recurrent multifocal osteomyelitis, and polyendocrinopathy, which might indicate a genetic basis. Unfortunately, most of these cases lack molecular genetic studies (33, 34). The present study was designed to emphasise the relationship between childhood LVV and genetic variants from phenotypic, genetic, and outcome perspectives. Given the nature of the study and the rarity of these entities, it was challenging to predetermine a set of variants or groups of genes. Therefore, in this study, all genetic variants were considered. Our review illustrated a spectrum of heterogenous disorders with various genetic variations, and then the LVV was determined. The most frequent underlying disorders associated with LVV were WAS and HIES. Notably, LVV is likely the result of a dysfunctional immune system and depending on the defect in the immune system, and probably other cofactors, it is appropriate to mention that identifying the mechanisms and phenotype and genotype associations is beyond the purview of this study. The LVV and IEIs' coincidence cannot be disregarded. Genetic factors may nevertheless play a role in the pathogenesis of vasculitis because, like most autoimmune diseases, its pathogenesis is poorly understood. Additionally, previous case reports make the other possibility of association or causation possible.

Table III. A summary of the clinical data of the published cases of large-vessel vasculopathy with genetic variants.

Reference	no. patients	Gender	Diagnosis	Age at disease onset	Age at diagnosis	Age at LVV diagnosis	Vascular findings	Abnormal imaging	Histopathology (Aorta)	Gene	Outcome
Van der Meer (7)	2	F	AR-HIES	NA	NA	19 years	Aneurysmal changes of AO, RA	MRI/ MRA	Media necrosis, infiltration of adventitial with plasmocytes	TYK2 Not done. (Expert diagnosis)	Died
		M				32 years	Aneurysmal changes of AO till brachiocephalic truncus	MRI/ MRA	multinucleated giant cells arteritis		Died
Inoue (9)	1	M	BS	7 months	7 years	3 years	left MCA stenosis AO aneurysm, bilateral RA stenosis	CTA	Not done	Heterozyg.NOD2 p.D382E mutation	Refractory, cerebral hemorrhage
Staels (14)	1	M	AR-HIGM	15 years	22 years	22 years	Active aortitis of ATO, AO till aortic bifurcation	PET–CT/ MRA	Not done	AICDA gene	Remission
Khubchandni (15)	1	F	BS	1 month	8 months	8 years	Stenosis aorta, carotids, left SCA, RA	CTA	Not done	NOD2 (G464W)	Remission on treatment
Lau (16)	1	M	WS	Infancy	4.5 years	5.5 years	Aortic aneurysm, stenosis of RA, mesenteric arteries	Angiography	Non done	WAS gene (X p11.22) Not done (Expert diagnosis)	Died
Van Son (17)	1	M	WAS	NA	Childhood	11 years	Aneurysmal dilatation, calcified ATO, AO	CTA	Lymphocyte, neutrophilic infiltrate	WAS gene (X p11.22) Not done (Expert diagnosis)	Remission
Johnston (18)	1	M	WAS	1 month	6 years	17 years	Dilatation AO,AA, DO	MRI	Destructive, full thickness, chronic aortitis inflammatory cells infilltration	WAS gene (X p11.22)	Surgical intervention
Onalan (19)	1	M	WAS	NA	Childhood	12 years	Aneurysmal dilatation of DO	CTA	Destructive, full thickness, chronic aortitis inflammatory cells infilltration	(X p11.22) (X p11.22)	Surgical intervention
Sargin (20)	1	F	FMF	16 years	17 years	17 years	Left ICA stenosis, hypoplastic left vertebral artery	MRA	Mononuclear cell infiltration seen in all the three layers	MEFV Het (M694V)	Surgical intervention
Zihni (21)	1	M	FMF	9 years	9 years	22 years	Stenosis of CCA, SCA, ATO, AO irregularities	Angiography	Non done	MEFV Compound Heterozygous (M694V/M726A)	Remission on treatment
Takeuchi (22)	1	M	XIAP deficiency	10 years	19 years	17 years	Wall thickness of aorta, major branches	CTA	Not done	XIAP (Hemizyg. c.1057-1G>A)	Remission post HSCT
Baek (23)	1	F	Marfan syndrome	Childhood	15 years	15 years	Aneurysm of aortic root, DO, left SCA, stenosis of left CCA, RA, SMA obstruction	CTA/ MRA	Not done	FIBN 1 Not done (Expert diagnosis)	Hemiplegia
Menon (24)	1	F	Noonan syndrome	Childhood	Childhood	9 years	Ascending aortic aneurysm	MRA	Zonal necrosis, intimal, adventitial scarring, giant cell infiltration	Expert diagnosis	NA
Borzutzky (25)	2	F	Noonan syndrome JMML	Infancy	18 months	9 years	Severe stenoses of DO and major branches	Angiography	Not done	Germline mutations in the CBL gene	Died
					14 months	14 months	Thickening of TO, suprarenal AO, celiac, SMA	MRI/PET–CT			Remission on treatment

Reference	no. patients	Gender	Diagnosis	Age at disease onset	Age at diagnosis	Age at LVV diagnosis	Vascular findings	Abnormal imaging	Histopathology (Aorta)	Gene	Outcome
Okada (26)	1	F	Familial hypercholesterolemia	15 years	15 years	15 years	Aortic arch, SCA, bilateral carotid arteries, dilation right SCA, diffuse narrowing AO	PET–CT/ MRA	Not done	LDL receptor gene deletion mutation (c.310_312del TGT/p.C104del)	Remission on treatment
	1	M	LRBA deficiency	NA	14 years	14 years	Wall thickness, focal dilatation of AO, complete occlusion RA	CTA	Not done	LRBA gene	Remission post HSCT
	1	M	XL-SCID	6 years	16 years	16 years	Fusiform aneurysmatic dilatation from DO, aortic wall thickening, irregularity, celiac, SMA stenosis	CTA	Not done	IL-2Rγ	Remission on treatment
	1	F	STAT1	Infancy	NA	NA	Dilation of left main coronary, dilatation AA, AO, severe calcinosis of vessel walls	CTA	Not dome	STAT1 gain of function missense mutation (c.862A > G; p.T288A)	NA

LVV: large-vessel vasculopathy; AR-HIES: autosomal recessive hyper IgE syndrome; NA: not available; AO: abdominal aorta; RA: renal artery; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; MCA: middle cerebral artery; CTA: computed tomography angiography; BS: Blau syndrome; AR-HIGM: autosomal recessive hyper IgM syndrome; WAS: Wiskott-Aldrich syndrome; FMF: familial Mediterranean fever; ATO: ascending thoracic aorta; DO: descending aorta; ICA: internal carotid artery; CCA: common carotid artery; SCA: subclavian artery; XIAP: X-linked inhibitor of apoptosis deficiency; SMA: superior mesenteric artery; JMML: juvenile myelomonocytic leukaemia; PET-CT: positron emission tomography-computed tomography; AA: aortic arch; LRBA: lipopolysaccharide-responsive and beige-like anchor protein; XL-SCID: X-linked severe combined immune deficiency; IL-2Rγ: interleukin 2 receptor gamma chain; STAT1: signal transducer and activator of transcription 1.

There was a marginal male preponderance, with 15 males and 10 females. The considerable interval between the onset of the underlying disorder and the diagnosis of LVV suggests that either this association is not well known, or it is a slow-progressing process. Our cohort contains the largest group of LVV with genetic variants, which may be influenced by significantly high consanguineous marriages. However, our clinical data was consistent with observations from previously published reports. Individuals with genetic variants took longer to be diagnosed with LVV than those without variants, which may have an impact on the severity of the disease and its prognosis.

All enrolled patients had imaging results that were consistent with vasculitis, either from computed tomography angiography (CTA) or magnetic resonance angiography (MRA). Evidently, imaging characteristics are insufficient as diagnostic methods for vasculitis. However, the cumulative data suggested LVV. Most patients with IEIs and autoinflammatory disorders like Blau syndrome had ongoing inflammatory processes manifested by elevated acute phase reactants, but few reports included such laboratory results; in that case, the term "vasculopathy," which denotes abnormal blood vessels caused by inflammation or genetic defects and leading to aneurysmal or stenotic changes with or without thrombosis, is appropriate. Disorders such as Marfan syndrome, familial hypercholesterolaemia, and Noonan syndrome are characterised by slowly progressive vascular changes and are thought to mimic vasculitis; however, inflammation might coexist with hereditary, non-inflammatory, or non-immune-mediated conditions (24-27). Two of our patients who exhibited high acute phase reactants and echocardiographic evidence of aortic dilatation also had a genetic confirmation of familial hypercholesterolemia due to a mutation in the low-density lipoprotein receptor (LDLR) gene. However, because there were no imaging studies (namely, CTA or MRA) or histopathological findings that could support vasculitis, we decided not to include them in our cohort.

A tissue biopsy is the confirmatory test for vasculitis. Unfortunately, most of the enrolled patients lacked a histopathology assessment. Our patients with genetic variants had elevated acute phase reactants, and three of them had proven histopathological findings. Interestingly, LVV has never been reported in patients with IPEX; one of our patients with the *FOXP3* variant initially presented with early-onset inflammatory bowel disease and was diagnosed with extensive aortitis and huge, inoperable aneurysmal changes. He was treated with biological agents, including an IL-6 inhibitor (tocilizumab). Unfortunately, he had progressive vascular changes and died suddenly at home. No autopsy was performed, but we believe that this might have been due to an aneurysmal rapture.

We noticed that patients with LVV and genetic variants required intensive immunosuppressive therapy, including HSCT, with substantial beneficial effects. Yet the mortality rate was high: 20% of the enrolled patients had a fatal outcome. It is crucial to remember that this was a heterogeneous group of patients. We believe that the underlying IEIs have a significant impact on the serious outcome.

This study has some limitations, and the findings should be interpreted carefully, particularly with a small sample size. The data is based on a retrospective analysis of collected data over a lengthy

period from various sources. Additionally, patients' selection cannot be biased. It was impossible to determine whether the genetic link was causal because of the nature of this study. Furthermore, despite the long-term assessment of the disease and accrual damage calculated, PVDI has not yet been validated.

In summary, our study identified rare and diverse forms of LVV in patients with genetic variants and presented a wide spectrum of clinical and laboratory findings. Accordingly, these findings allow us to propose "monogenic LVV" as a distinct umbrella to differentiate it from non-inherited LVV of unknown cause. This data study is intended to increase awareness of these entities among health care providers. Furthermore, it may help in developing different clinical approaches for such patients.

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