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University of Turku

Faculty of Medicine
Department of Internal Medicine
Doctoral programme in Clinical Research

Supervised by

Adjunct Professor Laura Pirilä
Centre for Rheumatology and
Clinical Immunology
Turku University Hospital
Department of Internal Medicine
University of Turku
Turku, Finland

Professor Jukka Kemppainen
Turku University Hospital
Department of Clinical Physiology and
Nuclear Medicine and Turku PET Centre
University of Turku
Turku, Finland

Reviewed by

Professor h.c. Tom Pettersson
University of Helsinki
Helsinki, Finland

Adjunct Professor Kalle Sipilä
Tampere University Hospital and
University of Tampere
Tampere, Finland

Opponent

Professor Ellen-Margrethe Hauge
Aarhus University Hospital and
University of Aarhus,
Aarhus, Denmark

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To my family

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ABSTRACT

The systemic vasculitides are characterized by inflammation of the blood vessel walls. Most vasculitides are idiopathic but sometimes a triggering event, e.g., medication, can be identified. Vessels of any type and size can be affected, resulting in a wide spectrum of symptoms ranging from mild to multisystemic life-threatening disorders. The rarity of vasculitides and the heterogeneous nature of the diseases present a diagnostic challenge causing diagnostic delay and numerous examinations. Imaging, including positron emission tomography with computed tomography (PET/CT), has an increasing role in the diagnostic work-up.

The aim of this study was to evaluate the performance of PET/CT prospectively, in a real-life cohort of patients with suspected vasculitis, to assess the diagnostic delay and total costs of the diagnostic process of systemic vasculitis and to explore the rare association between large vessel vasculitis (LVV), chemotherapy and granulocyte-colony stimulating factor (G-CSF).

PET/CT was found effective in diagnosing vasculitis in a cohort of 82 patients. Lower dose and shorter duration of glucocorticoid medication were significantly associated with positive PET/CT vasculitis finding. Overall, PET/CT revealed clinically significant information in 56% of the patients. Among systemic vasculitides, the diagnostic delay was substantial with great individual variability. Diagnostic delay was correlated with higher total costs, but PET/CT was not a significant contributor.

LVV and neutropenic infections might present with similar clinical symptoms. We identified six patients with breast cancer who unexpectedly developed acute, non-infectious LVV during chemotherapy. This patient series and a systematic literature review support the previous reports of a rare causal association between LVV, chemotherapy and G-CSF.

KEYWORDS: Systemic vasculitis, PET/CT, costs, diagnostic delay, drug-induced vasculitis, vasculitis

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
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TIIVISTELMÄ

Vaskuliitit ovat verisuonen seinämän tulehduksia, jotka immunologisella mekanismilla vaurioittavat suonen seinämää. Vaskuliitin syy on usein tuntematon, mutta joissain harvoissa tapauksissa laukaiseva tekijä, kuten lääkeaine, voidaan tunnistaa. Sairastuneen suonen koko ja sijainti vaikuttavat taudinkuvaan, joka vaihtelee lievistä paikallisoireista vaikeisiin elinvaurioihin. Vaskuliittien harvinaisuus ja oireiden epämääräisyys aiheuttavat diagnoosiviivettä ja laaja-alaisia tutkimuksia. Kuvantamistutkimuksilla, kuten positroniemissiotomografia-tietokonetomografialla (PET/TT), on lisääntyvä merkitys vaskuliittien diagnostiikassa.

Tämän tutkimuksen tarkoituksena oli selvittää PET/TT-kuvantamisen merkitystä vaskuliittiepäilyssä, systeemistä vaskuliittia sairastavien potilaiden diagnoosivaiheen viivettä ja kustannuksia sekä tutkia harvinaista yhteyttä suurten suonten vaskuliitin (SSV), kemoterapian ja valkosolukasvutekijähoidon välillä.

PET/TT osoittautui hyödylliseksi vaskuliittidiagnostiikassa. Glukokortikoidilääkityksen matalampi annos ja lyhyempi käyttöaika olivat merkitsevästi yhteydessä positiiviseen PET/TT-vaskuliittilöydökseen. PET/TT-kuvantamisessa 56 %:lla potilaista todettiin kliinisesti merkitsevä löydös. Potilailla, joilla oli systeeminen vaskuliitti, diagnoosiviive oli huomattava ja viiveen yksilöllinen vaihtelu suurta. Diagnoosiviiveen ja korkeampien kustannusten välillä oli merkittävä yhteys. Sen sijaan PET/TT ei ollut yksinään merkittävä kustannustekijä.

SSV ja neutropeeniset infektiot voivat olla taudinkuvaltaan samankaltaisia. Tunnistimme kuusi rintasyöpää sairastavaa potilasta, joille kehittyi yllättäen akuutti, ei-infektiivinen SSV kemoterapiahoidon aikana. Tämä potilassarja ja aiheesta laadittu systemaattinen kirjallisuuskatsaus puoltavat harvinaista syy-yhteyttä SSV:n, kemoterapian ja valkosolukasvutekijän välillä.

AVAINSANAT: Systeeminen vaskuliitti, PET/TT, diagnoosiviive, kulut, kustannukset, lääkkeen aiheuttama vaskuliitti, haittavaikutus, vaskuliitti

Table of Contents

Abbreviations

AAV	ANCA-associated vasculitis
ACR	American College of Rheumatology
ADR	Adverse drug reaction
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibody
C-GCA	Cranial-giant cell arteritis
CECT	Contrast enhanced computed tomography
CHCC	Chapel Hill Consensus Conference
COI	Cost of illness
CRP	C-reactive protein
CT	Computed tomography
CTA	Computed tomography angiography
CV	Cryoglobulinemic vasculitis
EGPA	Eosinophilic granulomatosis with polyangiitis
ENA	Extractable nuclear antigens
ESR	Erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
FDG	Fluorodeoxyglucose
GBM	Glomerular basement membrane
GC	Glucocorticoid
GCA	Giant cell arteritis
G-CSF	Granulocyte-colony stimulating factor
GPA	Granulomatosis with polyangiitis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HUV	Hypocomplementemic urticarial vasculitis
HUVS	Hypocomplementemic urticarial vasculitis syndrome
IQR	Interquartile range
KD	Kawasaki disease
LV-GCA	Large vessel-giant cell arteritis
LVV	Large vessel vasculitis

MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
PAN	Polyarteritis nodosa
PET	Positron emission tomography
PET/CT	Positron emission tomography/computed tomography
PR3	Proteinase 3
SD	Standard deviation
SLE	Systemic lupus erythematosus
TAB	Temporal artery biopsy
TAK	Takayasu arteritis
TNF	Tumor necrosis factor
US	Ultrasound

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Taimen K, Salomäki S, Hohenthal U, Mali M, Kajander S, Seppänen M, Nuutila P, Palomäki A, Roivainen A, Pirilä L, Kemppainen J. The clinical impact of using ^{18}F-FDG-PET/CT in the diagnosis of suspected vasculitis: the effect of dose and timing of glucocorticoid therapy. *Contrast Media & Molecular Imaging,* 2019 Aug; 2019. Doi:10.1155/2019/9157637.

II Taimen K*, Heino S*, Kohonen I, Relas H, Huovinen R, Hänninen A, Pirilä L. G-CSF- and chemotherapy-induced large-vessel vasculitis – six patient cases and a systematic literature review. *Rheumatology Advanced in Practice*, 2020;4:rkaa004. Doi: 10.1093/rap/rkaa004

III Taimen K, Mustonen A, Pirilä L. The delay and costs of diagnosing systemic vasculitis in a tertiary-level clinic. *Rheumatology and Therapy*, 2021;8:233-242. Doi:10.1007/s40744-020-00266-9.

*Equal contribution

1 Introduction

Vasculitis refers to an inflammatory process in the blood vessel walls. Vessels of any type and in any organ can be affected, resulting in a wide spectrum of symptoms and signs which can mimic manifestations of infectious, neoplastic, and autoimmune conditions. This makes the diagnosis a challenge and explains the long and variable diagnostic delays reported (Prior et al., 2017). Untreated vasculitis or incorrect diagnosis of vasculitis may result in harmful consequences, and therefore attempts should be made to establish an early and correct diagnosis. Imaging has enormously improved the diagnostics of systemic vasculitis, especially in giant cell arteritis (GCA). In 1999, the first report was published on the use of positron emission tomography (PET) in the diagnosis of large vessel GCA and polymyalgia rheumatica (Blockmans et al., 1999). Since then, numerous studies have confirmed the utility of PET, mostly combined with computed tomography (CT). However, in a real-world setting the patient cohorts are heterogeneous and diseases other than vasculitis may lie behind similar symptoms. In many cases, the patients are on glucocorticoid medication at the time of PET/CT scan and this is likely to interfere with the diagnostic accuracy of imaging (Nielsen et al., 2018). Large patient series are lacking due to the rarity of the vasculitides. As a result, it is less evident how PET/CT performs in a suspicion of vasculitis in everyday practice.

In the recent decades, an increasing number of diagnostic modalities have become available. Easy access to a variety of tests might facilitate the diagnostic work-up and shorten the diagnostic delay. On the other hand, some methods such as PET/CT, are expensive and may increase the costs of health care (Balink et al., 2015). Surprisingly little published data is available regarding the direct or indirect expenses of the diagnostic process of vasculitis. In addition, comparison of the economic burden between different health care systems is difficult. When evaluating the diagnostic protocols, it would be helpful to have cost assessments representing the realistic perspective.

In most cases of vasculitis, the triggering event remains unknown. Therefore, identification of the possible underlying condition might have an immense positive impact on treatment guidance. For example, in drug-induced vasculitis, withdrawal

of the offending drug may alone be sufficient to induce prompt resolution of vasculitis symptoms (Grau, 2015).

In this thesis project, we evaluated the feasibility of PET/CT to diagnose systemic vasculitis in a real-life cohort of patients, explored the diagnostic delay and costs of diagnosing systemic vasculitis and reported a probable new type of drug-induced vasculitis in a form of a patient series and a systematic literature review.

2 Review of the Literature

2.1 Systemic vasculitis: Nomenclature and classification

The systemic vasculitides are a group of disorders characterized by blood vessel inflammation, which lead to tissue or end organ injury. In order to improve their categorizing and naming, the first International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides was held in 1994 (CHCC1994) (Jennette et al., 1994). Since then, CHCC has been the most used nomenclature for primary systemic vasculitis. The nomenclature and definition system has changed over the years and the most recent revision is from the 2012 (Jennette et al., 2013). Among the remarkable changes in CHCC 2012 were the replacement of eponyms with disease names that reflect the pathophysiology of these conditions. Some important name modifications were eosinophilic granulomatosis with polyangiitis (EGPA; previously Churg-Strauss syndrome), granulomatosis with polyangiitis (GPA, previously Wegener's granulomatosis), immunoglobulin A (IgA) vasculitis (IgAV, previously Henoch-Schönlein purpura) and anti-C1q vasculitis as an optional name for hypocomplementemic urticarial vasculitis. Also, the term antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis (AAV) was adopted for the group of three disorders that include EGPA, GPA and microscopic polyangiitis (MPA).

Besides nomenclature, the classification of the systemic vasculitides has been controversial for decades. In 1990 the American College of Rheumatology (ACR) published criteria for the classification of seven types of vasculitis (Fries et al., 1990; Hunder et al., 1990) but these criteria are generally accepted to be outdated. ACR 1990 criteria were developed before ANCA testing and modern imaging were introduced. CHCC is mainly a nomenclature system, but it also includes widely accepted definitions for vasculitis. Overall, classification of the noninfectious vasculitides is primarily based upon the predominant size of the vessels involved. The term 'large vessel' refers to the aorta and its major branches, 'medium vessels' relates to the main visceral arteries, veins and their proximal branches, and 'small vessels' refers to arterioles, capillaries, intraparenchymal arteries, venules and some veins (Jennette et al., 2013). The 2012 CHCC definitions emphasized that vasculitis may involve other vessel sizes outside the dominant vessel size (e.g., large vessel vasculitis may overlap

with medium-sized vessel vasculitis). The 2012 CHCC revision introduced a new category- variable-vessel vasculitis- to include Behçet's disease and Cogan's syndrome into the vasculitis spectrum and developed definitions for single-organ vasculitis. Existing classification criteria are still controversial, which is why the Diagnostic and Classification Criteria of Vasculitis study (DCVAS) aims to provide new validated criteria for systemic vasculitis (Craven et al., 2013).

Table 1. Nomenclature of vasculitis defined by 2012 International Chapel Hill Consensus Conference.

Small-vessel vasculitis (SVV)	Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)	Microscopic polyangiitis (MPA)
		Granulomatosis with polyangiitis (Wegener's) (GPA)
		Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
	Immune complex SVV	Anti-glomerular basement membrane (anti-GBM) disease
		Cryoglobulinemic vasculitis (CV)
		IgA vasculitis (IgAV, Henoch-Schönlein)
		Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
Medium-vessel vasculitis (MVV)	Polyarteritis nodosa (PAN)	
	Kawasaki disease (KD)	
Large-vessel vasculitis (LVV)	Takayasu arteritis (TAK)	
	Giant cell arteritis (GCA)	
Variable vessel vasculitis (VVV)	Behçet's disease (BD)	
	Cogan's syndrome (CS)	
Single-organ vasculitis (SOV)	Cutaneous leukocytoclastic angiitis	
	Cutaneous arteritis	
	Primary central nervous system vasculitis	
	Isolated aortitis	+others
Vasculitis associated with systemic disease	Lupus vasculitis	
	Rheumatoid vasculitis	
	Sarcoid vasculitis	+others
Vasculitis associated with probable etiology	Hepatitis B and C-virus associated vasculitis	
	Drug-associated vasculitis	
	Cancer associated vasculitis	+others

Adopted from Jennette et al. 2013

2.2 Systemic vasculitis: Overview of epidemiology, etiopathogenesis and clinical presentation

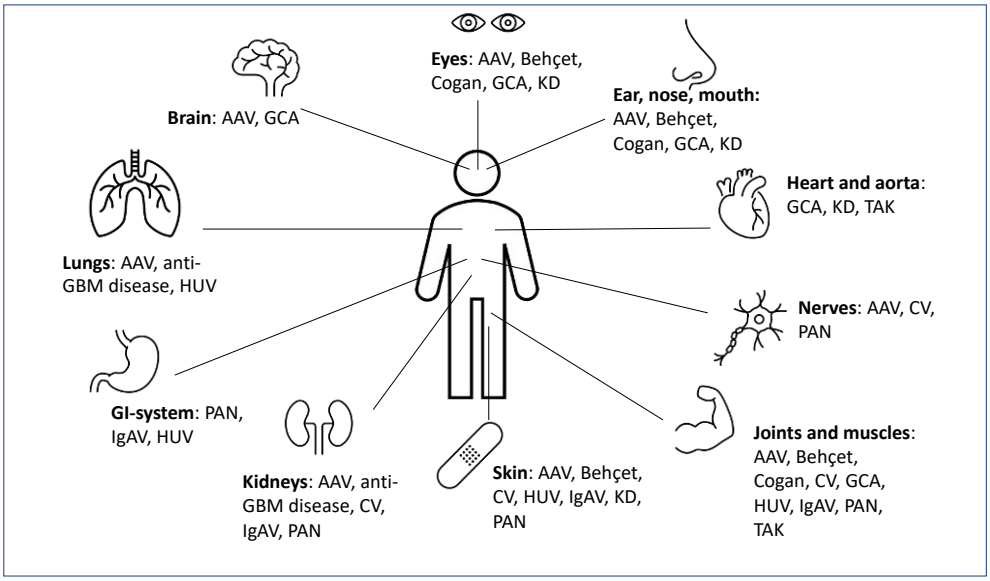

Figure 1. Common areas of manifestations of different vasculitides. AAV: ANCA-associated vasculitis; anti- GBM disease: anti- glomerular basement disease; CV: cryoglobulinemic vasculitis; GCA: giant cell arteritis; HUV: hypocomplementemic urticarial vasculitis; IgAV: IgA vasculitis; KD: Kawasaki disease; PAN: polyarteritis nodosa; TAK: Takayasu arteritis.

2.2.1 Large-vessel vasculitis

Large-vessel vasculitis affects mostly large arteries, mainly aorta and its major branches. Takayasu arteritis (TAK) and giant-cell arteritis (GCA) are the two major variants (Jennette et al., 2013).

2.2.1.1 Takayasu arteritis

TAK is a rare vasculitis that was first described in Japan and is considered most common in individuals of Asian ancestry. The highest prevalence is reported in Japan, 40 per million (Toshihiko, 1996). In Europe, the annual incidence rate is estimated to be 1–2 per million (Gudbrandsson et al., 2017). Women are affected in 80–90% of cases with age at onset between 10 and 40 years (Lupi-Herrera et al., 1977).

The pathogenesis of TAK is not well understood. Granulomatous vasculitis is a typical pathological finding and may be similar to GCA (Weyand & Goronzy, 2003).

Cell-mediated mechanisms are thought to be most important. The inflammatory process characteristically involves the inner layers (tunica intima and media) of the blood vessel walls, progressing from granulomatous inflammation to less obvious reaction in the later stages of the disease in which adventitial fibrosis, intimal proliferation and vessel stenosis predominate (Zaldivar Villon et al., 2019). The initial vascular lesions often occur in the subclavian arteries (Mason, 2010).

TAK is characterized by a chronic, waxing and waning clinical course that is dominated by non-specific constitutional and systemic symptoms in the early phase. As the disease progresses, the vascular ischemic symptoms are more dominant due to narrowing, occlusion, and dilatation of the vessels. Common early symptoms are low-grade fever, weight loss, arthralgias or arthritis, myalgia, and fatigue. The ischemic process may lead to limb claudication, cyanosis, brachial pulse deficit, blood pressure discrepancy and arterial bruits which are critical characteristics for classifying patients with TAK. Coronary vessel stenosis may develop in 25% of the patients and aortic regurgitation in 5–55%. (Sanchez-Alvarez et al., 2019; Zaldivar Villon et al., 2019).

2.2.1.2 Giant cell arteritis

GCA is the most common idiopathic systemic vasculitis involving especially the supra-aortic large- and medium sized vessels including temporal arteries and aorta (Weyand & Goronzy, 2014). The greatest risk factor is age, since most patients are over 50 years old and the peak incidence is between 70 and 79 years of age (Gonzalez-Gay et al., 2009). GCA is more common in women with a female to male ratio of 3:1. The highest incidence figures are found among individuals of Scandinavian descents, 17–43 per 100,000 persons over the age of 50 (Gonzalez-Gay et al., 2009; Sharma et al., 2020). In Southern Europe, the incidence rates are lower, approximately 10 per 100,000 persons over the age of 50 (Gonzalez-Gay et al., 2007). Genetic studies have shown a strong association between GCA and human leucocyte antigen (HLA) DRB1*04 alleles (Carmona et al., 2015). The nature of the triggering agent(s) is still uncertain. Based on periodic increases in incidence, some epidemiological studies suggest environmental factors play a role. Varicella-zoster virus sequences have been detected in temporal artery biopsies but no clear causal relationship has been demonstrated (Koster & Warrington, 2017).

GCA is considered a prototypic granulomatous disease with T cells and macrophages as major drivers of pathology (Samson et al., 2017; Weyand & Goronzy, 2003). An unknown trigger activates the dendritic cells (DC) localized in the adventitia of normal arteries (Watanabe et al., 2016). Activated DCs then produce chemokines, which trigger the recruitment of CD4+ T cells. These proliferate and polarize into Th1 and Th17 cells, which produce interferon (IFN)-gamma and

interleukin (IL)-17, respectively. Continuous IFN-gamma exposition stimulates macrophages which may give rise to multinucleated giant cells aligned along the internal lamina elastica. Macrophages located in the adventitia produce IL-6 and IL-1ß, which are the main drivers of the constitutional symptoms of GCA. The medial layer of the inflamed arteries is invaded by the inflammatory cells resulting in a substantial loss of vascular smooth muscle cells. The response to inflammation leads to vascular remodeling resulting in intimal hyperplasia and disturbed blood flow causing ischemia (Samson et al., 2017; Watanabe et al., 2016; Weyand & Goronzy, 2003).

The clinical presentation of GCA is heterogenous and is based on the distribution of vascular involvement. New, often persistent and severe, headache is a common presentation in more than 2/3 of patients (Gonzalez-Gay et al., 2005). Other common cranial symptoms are jaw claudication (about 50% of the patients), scalp tenderness and beaded or tender temporal artery with decreased pulse (Buttgereit et al., 2016). Ischemic ocular involvement causing optic neuropathy resulting in sudden, often permanent, vision loss is reported in 8 to 15% of patients (Chen et al., 2016). Other ocular symptoms may be amaurosis fugax (transient visual loss) and diplopia. Large-vessel GCA (LV-GCA), a subset of GCA, affects large, supra-aortic arteries, their branches and/or the aorta. These patients might not have the classical cranial symptoms (de Boysson et al., 2019). Overall, the onset of symptoms is often subacute. Many clinical manifestations are non-specific, but the combination of characteristic findings may suggest the diagnosis. Systemic symptoms, such as fever, weight loss, fatigue and night sweats are frequent (Buttgereit et al., 2016). Polymyalgia rheumatica (PMR) and GCA are related inflammatory disorders. Typical polymyalgia symptoms are symmetric proximal polyarthralgia and myalgias. Approximately 50% of patients with GCA present with PMR symptoms before, at the time of, or after the diagnosis of vasculitis (Weyand & Goronzy, 2014). Upper limb claudication can result from inflammation-related arterial stenosis. Aortic inflammation usually presents with constitutional symptoms and may result in the formation of aneurysm that cause thoracic, abdominal and/or back pain. If complicated, intramural hematoma, dissection or rupture can occur (Buttgereit et al., 2016). Stroke, cranial nerve palsy, and scalp necrosis are rare ischemic complications (Weyand & Goronzy, 2014). Aortic valve insufficiency may develop.

2.2.2 Medium-vessel vasculitis

Medium-vessel vasculitis (MVV) affects primarily the main visceral arteries and their proximal branches. Kawasaki disease (KD) and polyarteritis nodosa (PAN) are the two types of medium vessel-vasculitis (Jennette et al., 2013;Watts & Robson, 2018).

2.2.2.1 Kawasaki disease

KD is a one of the most common childhood vasculitides affecting primarily children younger than 5 years of age. Asian ancestry populations have the highest incidence of KD; in Japan the annual incidence rate was 264 per 100,000 population aged 0–4 years (Makino et al., 2015). In England, the incidence within the same age group was 8 per 100,000 (Harnden et al., 2009). It seems to be more common in boys than girls (Watts & Robson, 2018).

The etiology of KD remains unknown but an infectious etiology has long been suspected since the seasonal variations and epidemics have been reported (Watts & Robson, 2018). KD affects the medium-sized arteries of which the coronary arteries are the most significant ones. Vessel injury appears to result from inflammatory cell infiltration into vascular tissues causing destruction of collagen fibers and elastin and loss of structure, leading to dilatation and aneurysm formation. Affected tissues in KD are characterized by granulomatous inflammation that consists of accumulation of monocyte-macrophages. IgA producing plasma cells are present (Rowley & Shulman, 2010). The release of pro-inflammatory cytokines, such as TNF and IL-1ß, promotes vascular endothelial cell damage (Rowley & Shulman, 2010).

The diagnosis of KD is based on the presence of systemic inflammation in association with mucocutaneous inflammation. Fever is the cardinal manifestation of KD. Bilateral, non-purulent conjunctivitis is present in over 90 percent of the patients. Mucositis, such as cracked, red lips and "strawberry" tongue, becomes more evident as KD proceeds. Polymorphous exanthema usually begins early in the disease. Changes in the extremities such as swelling, and redness of the palms and desquamation occur in the later phases of KD. Cervical lymphadenopathy is present in some children (April et al., 1989). Typical KD is defined if patient presents with ≥4 aforementioned symptoms and fever. (Dietz et al., 2017). Cardiovascular symptoms are not part of the diagnostic criteria although improved echocardiographic techniques have revealed coronary artery dilatation in 30% of patients at diagnosis (Printz et al., 2011).

2.2.2.2 Polyarteritis nodosa

PAN is the predominant medium-vessel vasculitis in adults. The disease is uncommon with the incidence of 1–10 per million (Watts, 2001). There is a slight 1:1.5 male predominance. Most patients are middle-aged with a peak incidence between 50 and 60 years (Pagnoux et al., 2010). The etiopathogenesis is linked to viral hepatitis infection and the worldwide reduction in hepatis B virus (HBV) -infection has been associated with a decreased prevalence of PAN (Pagnoux et al., 2010).

Most cases of PAN are idiopathic but in some cases hepatitis C infection (HCV), HBV and hairy cell leukemia play an important role in the pathogenesis. If the pathogen is confirmed, PAN is considered a secondary disease. The pathogenetic mechanism of PAN is poorly understood and in some cases PAN might represent more of a spectrum of disease (Ozen, 2017). Endothelial injury, through immune complex deposition and viral replication, has been proposed as an important trigger in HBV-related PAN (Farrah et al., 2019). However, this does not explain the majority of PAN which is not infection related. Regardless of the underlying cause, PAN is characterized by transmural, segmental necrotizing inflammation of muscular arteries and sparing the veins (Ozen, 2017). Internal and external elastic lamina are damaged and may lead to development of aneurysmal dilatation (De Virgilio et al., 2016). Granulomatous inflammation is not usual in PAN, and it should suggest other diagnoses. In recent years, mutations in specific genes, such as adenosine deaminase 2 (ADA2), have been shown to be associated with a necrotizing vasculopathy similar to PAN (Ozen, 2017).

PAN typically presents with systemic symptoms. The disease spectrum ranges from single organ involvement to multisystem failure. Virtually, any organ can be affected, but for unknown reasons PAN does not affect the lungs (De Virgilio et al., 2016). Common systemic symptoms are fever, weakness, weight loss, myalgia, arthralgia, and fatigue. The peripheral nervous system, skin and kidneys are the most frequently involved areas (Pagnoux et al., 2010). Skin manifestations may include purpura, livedoid lesions, subcutaneous erythematous nodules and necrotic ulcers (De Virgilio et al., 2016; Pagnoux et al., 2010). In autopsy studies, the kidneys are one of the most commonly involved organs which may lead to renal insufficiency and hypertension (De Virgilio et al., 2016). The most common neurological symptom is mononeuritis multiplex, which presents with foot or wrist drop. Sometimes symmetrical polyneuropathy also occurs (Rossi & Di Comite, 2009). The gastrointestinal tract is frequently involved, and these manifestations are among the severe expressions of PAN. Abdominal pain might be an early symptom of mesenteric arteritis. Other possible symptoms are nausea, vomiting, diarrhea, gastrointestinal bleeding and intestinal perforation and peritonitis (Levine et al., 2002). Unilateral orchitis due to the testicular artery ischemia is seen as a characteristic symptom of PAN (De Virgilio et al., 2016). Hearing loss has been described as an otological manifestation of PAN (De Virgilio et al., 2016).

2.2.3 Small-vessel vasculitis

Small-vessel vasculitis (SVV) predominantly affects the small vessels, defined as small intraparenchymal arteries, arterioles, capillaries, and venules. Medium arteries may be affected. SVV include the ANCA-associated vasculitides (AAV) which are

EGPA, GPA and MPA as well as immune complex SVV which are IgAV, cryoglobulinemic vasculitis, anti-glomerular basement membrane (GBM) disease (Goodpasture syndrome) and hypocomplementemic urticarial vasculitis (HUV) (Jennette et al., 2013; Watts & Robson, 2018).

2.2.3.1 ANCA-associated vasculitis

AAV is a rare disease with a global reported annual incidence ranging from 1.2 to 2.0 cases per 100,000 persons (Watts et al., 2015). Among the AAV patients, EGPA (previously called Churg-Strauss syndrome) is the least common with an incidence of 0.4 per 100,000. For GPA, the US study reported an incidence of 1.3, and for MPA an incidence of 1.6 per 100,000, respectively (Berti et al., 2017). AAV can occur at any age but mostly after the age of 55. Both sexes are affected (Hunter et al., 2020). It is important to note that the term "ANCA-associated vasculitis" may sometimes be misleading since in 10% of patients with clinically and histopathologically proven diagnoses of AAV no ANCAs can be demonstrated (Nakazawa et al., 2019).

The etiopathogenesis of AAV is multifactorial. The events that may lead to the initiation of AAV include genetic factors, infections, and environmental factors, including drugs. Genome-wide association studies have identified several genes of either resistance or susceptibility to AAV (Lyons et al., 2012). Because infection-like symptoms are frequently noted to precede AAV, identification of pathogens, e.g. Staphylococcus aureus, has been explored (Popa & Tervaert, 2003). Other factors, such as ultraviolet radiation, silica and levamisole-adulterated cocaine, have been studied (Watts et al., 2015). Neutrophils are key players in the acute phase of AAV. Vascular inflammation is induced when resting neutrophils having ANCA autoantigens, mainly myeloperoxidase (MPO) or proteinase 3 (PR3), are exposed to priming factors that cause the release of ANCA antigens on the surface of neutrophils (Cornec et al., 2016; Davies et al., 1982). ANCA binding to antigens activates neutrophils which leads to release of inflammatory cytokines, reactive oxygen species, lytic enzymes, and activation of the alternative complement pathway. Neutrophil extracellular traps (NET), which are produced in excessive quantities by neutrophils activated by ANCA, also contribute to ANCA production, thus creating a vicious circle (Nakazawa et al., 2019). The precise mechanisms by which ANCAs arise remain unclear. PR3-ANCAs are associated with GPA. The majority of patients with MPA have MPO-ANCAs and less than half of the patients with EGPA present with MPO-ANCAs (Cornec et al., 2016). PR3+ disease is frequently associated with higher rates of relapses (Farrah et al., 2019). Besides being biomarkers, ANCAs have pathogenic potential themselves (Jennette & Falk, 2014). Histologically pauci-

immune necrotizing and crescentic glomerulonephritis is related to all AAV (Nakazawa et al., 2019).

AAV may present with constitutional symptoms, such as fever, weight loss, fatigue, night sweats, polyarthralgia or myalgia, or with specific features of end-organ involvement. GPA typically affects the upper and lower respiratory tract and kidneys and is characterized by granulomatous inflammation with necrosis. Presenting ear-nose-throat (ENT) symptoms include nasal discharge or crusting, oral/nasal ulcers, otitis media or hearing loss. Lower respiratory tract manifestations include dyspnea, cough, hemoptysis, stridor, or pleuritic pain. MPA presents with glomerulonephritis and pulmonary capillaritis. Histopathology shows necrotizing vasculitis without granulomatous inflammation. EGPA is characterized by allergic rhinitis, asthma, and peripheral blood eosinophilia. However, almost any part of the body can be affected in AAV. Peripheral neuropathy may present as weakness, numbness or foot or wrist drop. On the skin, purpura is frequent. Other symptoms may include painful, red eyes caused by scleritis or orbital pseudotumor (Conron & Beynon, 2000; Hunter et al., 2020; Jennette et al., 2013; Kallenberg, 2014; Yates & Watts, 2017). The symptoms can progress slowly over months or rapidly within a few days. Patients may relapse with manifestations, which may be different from the initial presentation (Wallace & Miloslavsky, 2020).

2.2.3.2 IgA vasculitis

IgA vasculitis (IgAV; formerly called Henoch-Schönlein purpura) is the most common systemic vasculitis in children (Jennette et al., 2013). The annual incidence in children ranges from 3.5 to 27.6 per 100,000. The peak incidence is in children between the ages of 4 to 6 years (Watts & Robson, 2018). IgAV is much less frequent in adulthood. In France, the incidence of IgAV is estimated to be 0.1–14 per 100,000 adults (Deshayes et al., 2017). Studies have found a male predominance, approximately 1:1.2–1:1.8 (Hočevar et al., 2014).

IgAV is an immune-mediated vasculitis associated with abnormal IgA depositions in vessel walls (Jennette et al., 2013). Although a variety of infections, such as upper respiratory tract or gastrointestinal tract infections, and chemical triggers are recognized, the underlying cause remains unknown. Interplay of genetic, environmental and immunologic factors seems to play a role (Rigante et al., 2013).

Typically, IgAV involves the gastrointestinal tract and skin and causes arthritis. The classic tetrad includes abdominal pain, arthralgia (or arthritis), palpable purpura and renal disease (Du et al., 2020). Adults and children have similar symptoms with the exception that adults are at an increased risk of developing severe renal disease. The most common presentation of renal disease is hematuria in combination with mild proteinuria (Du et al., 2020). Almost any part of the gastrointestinal tract might

be affected but small bowel manifestations are most common (Audemard-Verger et al., 2020). The symptoms may develop over days or weeks and their order of appearance varies.

2.2.3.3 Cryoglobulinemic vasculitis

Cryoglobulinemic vasculitis (CV), previously called essential cryoglobulinemic vasculitis, refers to a systemic inflammatory disease in small-to-medium vessels caused by cryoglobulin-containing immune complexes. It is a rare form of vasculitis whose incidence and prevalence are unknown (Watts & Robson, 2018).

Cryoglobulins are serum and plasma proteins that precipitate in low temperatures and dissolve upon rewarming (Ramos-Casals et al., 2012). They are either immunoglobulins (Igs) or a mixture of Igs and complement components. Cryoglobulinemia is related to various diseases, which can be widely grouped into autoimmune conditions, infections and malignancies; the most frequent cause is infection with HCV (Ramos-Casals et al., 2012).

The major clinical manifestations of CV include systemic symptoms such as weakness, fatigue and palpable purpura (which is common in many forms of small-vessel vasculitis), renal disease, arthralgia and peripheral neuropathy (Jennette et al., 2013). In an Italian study, the clinical triad of purpura, weakness and arthralgia (Meltzer's triad) was present in 80% of patients (Ferri et al., 2004). Different manifestations may occur at different times in an individual patient. Suspicion of CV should arise when a patient with symptoms of vasculitis has low complement 4 and high levels of rheumatoid factor (Ferri et al., 2004; Gorevic, 2012).

2.2.3.4 Anti-GBM disease

Anti-glomerular basement membrane (GBM) disease (Goodpasture syndrome) is a small-vessel vasculitis that involves glomerular capillaries causing rapidly progressive renal failure often in combination with pulmonary capillaritis leading to alveolar hemorrhage. There is an ongoing discussion whether anti-GBM disease is a vasculopathy or a genuine vasculitis (Watts & Robson, 2018). An Irish study estimated the national incidence to be 1.64 per million population per year (Canney et al., 2016). The same study reported temporal and spatial clusters of cases suggesting an environmental trigger for disease onset. The peak incidence is in the third decade and in the sixth to seventh decade of life (Fischer & Lager, 2006).

In anti-GBM disease the antibodies are targeted against an antigen intrinsic to the GBM and alveolar basement membrane. In kidney biopsies, patients have severe necrotizing glomerulonephritis often with crescents (Fischer & Lager, 2006).

Sometimes patients also present with ANCA, which raises the possibility of an overlap with AAV (Watts & Robson, 2018).

Most patients present with rapidly progressive glomerulonephritis occurring sometimes as fast as in days or weeks (Canney et al., 2016; Gulati & McAdoo, 2018). A brief prodromal phase with systemic complaints and signs such as malaise, fever, and arthralgia, is present typically less than 2 weeks. In the early stages the symptoms may be nonspecific but with disease progression features of renal failure may develop. Approximately 50% of the patients need renal replacement therapy at the time of diagnosis (Gulati & McAdoo, 2018). Diffuse alveolar hemorrhage presenting with dyspnea, hemoptysis or respiratory failure has been reported in 20-60% of patients (Lazor et al., 2007).

2.2.3.5 Hypocomplementemic urticarial vasculitis

Hypocomplementemic urticarial vasculitis (HUV; also called anti-C1q vasculitis) is a vasculitis involving small vessels that is accompanied by urticaria. Hypocomplementemia and anti-C1q antibodies are present (Jennette et al., 2013). The terminology of HUV and hypocomplementemic urticarial vasculitis syndrome (HUVS) is overlapping. Based on some studies, HUVS is recognized as a specific autoimmune condition presenting with over six months of urticaria, with hypocomplementemia, together with diverse systemic, defined findings (Alomari et al., 2019). There is little data on the epidemiology of HUV/HUVS. In Sweden the annual incidence was 0.7 per million and the median age of onset 51 years (Watts & Robson, 2018).

HUV is believed to result from formation of immune complexes that deposit in vessel walls. HUV is associated with some disorders in which the antigen-antibody complexes are well defined (e.g., HBV, HCV). Besides viruses, some medications are suspected to trigger HUV (Bulva & Simon, 2017). Histological examination shows a leukocytoclastic vasculitis with fibrinoid deposits and damage of the vessel wall. Perivascular and basement membrane zone deposits of immunoglobulin or complement are present (Bulva & Simon, 2017).

Since the diagnosis of urticarial vasculitis requires clinical urticaria, the urticarial plaques are present in all patients. Compared with the common urticaria, the plaques in HUV/HUVS last longer (>24 hours) and are often tender and with a burning sensation. Other common manifestations include arthralgia, pulmonary involvement in many forms (such as cough, dyspnea, asthma, chronic obstructive pulmonary disease, pleurisy), gastrointestinal symptoms in 30% of patients (such as nausea, pain, diarrhea) and ocular symptoms (such as episcleritis and uveitis) (Alomari et al., 2019; Bulva & Simon, 2017). Renal disease presents with hematuria and proteinuria suggesting glomerulonephritis and was present in 14% of the patients in a French

cohort (Jachiet et al., 2015). Angioedema is fairly common (Jachiet et al., 2015). In rare cases, cardiac and neurological symptoms have been reported (Bulva & Simon, 2017).

The terminology of HUV/HUVS is variable. However, patients with HUV have more limited disease with cutaneous symptoms and a few or no systemic manifestations. Since the clinical presentation is nonspecific, the diagnosis requires demonstration of leukocytoclastic vasculitis in skin biopsy. Blood testing shows hypocomplementemia and anti-C1q antibodies (Bulva & Simon, 2017).

2.2.4 Variable vessel-vasculitis

Variable vessel-vasculitis (VVV) can affect vessels of any size (small, medium, and large) and any type of vessels (capillaries, veins, and arteries). In 2012, Behçet's disease and Cogan's syndrome were included as primary vasculitides in CHCC nomenclature (Jennette et al., 2013).

2.2.4.1 Behçet's disease

Behçet's disease (BD, or Behçet's syndrome) is a rare systemic inflammatory disorder presenting with recurrent aphthous oral ulcers, genital ulcers, and ocular inflammation. There is a large variation in prevalence between populations, with the highest rates in the region between eastern Mediterranean countries and China, along the ancient Silk Road (Watts & Robson, 2018). It is the most common in Turkey, where the pooled prevalence is 120/100,000 inhabitants. In Europe, the estimated prevalence is 3.3/100,000 (Watts & Robson, 2018). The most affected are young adults between 20 to 40 years of age. The prevalence is similar in men and women but the disease seems to be more severe in young males (Kural-Seyahi et al., 2003).

The etiology of BD is unknown (Zeidan et al., 2016). The pathogenesis probably implies an unknown infectious agent, which triggers an aberrant inflammatory response in a genetically susceptible host (Marshall, 2004). Histopathological studies classically show necrotizing vasculitis and venous thrombosis with lymphocytic infiltration in vessels of all sizes (Zeidan et al., 2016).

BD may involve nearly all vascularized systems (Bettiol et al., 2019). It is characterized by recurrent oral aphthous ulcers, genital sores, and ocular inflammatory lesions. Painful oral ulcers are typically the first manifestation of BD. Painful genital ulcers are present in 75% of patients. Ocular disease, involving the retina and the uvea and possibly leading to blindness, occurs in 30–70% of patients and is associated with high morbidity (Zeidan et al., 2016). Cutaneous manifestations are common and include acneiform lesions, erythema nodosum and pathergy reaction (Zeidan et al., 2016). Non-erosive arthritis (or arthralgia) is present in about

one half of patients and most commonly affects large and medium-sized joints (Zeidan et al., 2016). Other less common manifestations are variable neurological symptoms (in 5–10% of patients), miscellaneous pulmonary findings and cardiovascular symptoms, such as pericarditis or deep vein thrombosis (Zeidan et al., 2016). Gastrointestinal manifestations are present in 3–26% of patients and include anorexia, nausea and diarrhea, sometimes mimicking the symptoms of inflammatory bowel disease (Marshall, 2004).

2.2.4.2 Cogan's syndrome

Cogan's syndrome (CS) is a rare, chronic inflammatory disorder most often affecting young adults. The peak incidence is in the third decade of life (Espinoza et al., 2020). Hallmarks of the disease are interstitial keratitis and vestibuloauditory dysfunction. Vasculitis may occur in some patients with CS (Jennette et al., 2013).

The etiology and pathogenesis of CS are not understood. Because autoantibodies against corneal structures and inner ear antigens have been detected and the clinical response to immunosuppressive medication is favorable, it is considered to be an autoimmune disease (Durtette et al., 2017; Espinoza et al., 2020). In the eye, the very characteristic interstitial keratitis is caused by the inflamed small blood vessels invading the normally avascular corneal stroma (Cogan & Kuwabara, 1989). Overall, pathologic findings are relatively nonspecific and compatible with a chronic inflammatory process.

CS can be categorized into two groups based on onset of symptoms. Diagnosis of typical CS is made when vestibuloauditory and ocular symptoms present within 2 years of each other. If there is a delay of more than 2 years between those symptoms, atypical CS is diagnosed (Espinoza et al., 2020). The distinctive interstitial keratitis presents with symptoms of photophobia, eye redness, blurred vision, and pain. Sometimes other parts of the eye may be involved (Espinoza et al., 2020). The inner ear manifestations are Ménière-like attacks of vertigo, nausea, ataxia, tinnitus and hearing loss and recurrent episodes may result in profound sensorineural hearing loss (Durtette et al., 2017; Espinoza et al., 2020). The systemic disease form affects about 80% of patients with the majority of patients presenting with constitutional symptoms of weight loss, fever, arthralgia and myalgia (Durtette et al., 2017). When present in CS, systemic vasculitis is an aortitis, or in some cases less specific vasculitis in smaller vessels (Colodetti et al., 2017; Espinoza et al., 2020).

2.2.5 Other vasculitides listed by 2012 CHCC

The previously described vasculitides are mostly systemic vasculitides. However, the 2012 CHCC nomenclature also includes single-organ vasculitis (SOV), vasculitis

associated with systemic disease and vasculitis associated with probable etiology (Jennette et al., 2013).

SOV is vasculitis in arteries or veins of any size in a single organ. There should not be signs indicating that it is a limited form of a systemic vasculitis. The nomenclature includes the involved organ and vessel type (e.g. primary central nervous system vasculitis or isolated aortitis) (Jennette et al., 2013). Sometimes patients initially diagnosed with SOV may develop further manifestations requiring re-evaluation for systemic vasculitis.

Vasculitis can be caused by or be associated with a systemic disease such as systemic lupus erythematosus or sarcoidosis. These are often considered to be secondary vasculitides (Jennette et al., 2013). Most often they affect the small vessels.

Some vasculitides are associated with a probable specific etiology and they should have a prefix specifying the association (e.g. HBV-associated polyarteritis nodosa or cancer-associated vasculitis) (Jennette et al., 2013).

2.3 Diagnostic tools for vasculitis

Manifestations of vasculitis are heterogenic in severity and organ distribution so there is no single method or algorithm for all vasculitides. The clinical suspicion is the key for diagnosis. Vasculitis should be considered if patient presents with systemic symptoms in combination with evidence of single or multiorgan dysfunction. Outlines of clinical symptoms of main vasculitides are described in *Chapter 2.2.* When the diagnosis remains uncertain, observation over time, a therapeutic trial and repeated investigation may increase the probability of the vasculitis diagnosis or lead to another diagnosis (Jayne, 2009; Miloslavsky et al., 2017).

2.3.1 Laboratory investigations

Laboratory tests are often necessary to confirm the systemic inflammation, further investigate the degree of organ involvement, or identify another disease. The extent and speed of initial laboratory evaluation depends on the severity of the manifestations. However, often the raised inflammatory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are key findings showing non-specific systemic inflammation. When there is a suspicion of vasculitis, other early phase laboratory investigations include a complete blood count (CBC), serum creatinine, liver function studies, urinalysis and blood cultures to exclude infection (Jayne, 2009; Miller et al., 2010; Weyand & Goronzy, 2014). Other recommended initial investigations and their timing may vary slightly from expert to expert. In

2009, Jayne recommended as initial laboratory tests serologies for viral hepatitis, serum cryoglobulins, clotting screen, urea, electrolytes, immunoglobulins, protein electrophoresis, ANCA, antinuclear antibodies (ANA), extractable nuclear antigens (ENA) antibodies, rheumatoid factor, complement concentrations (C3, C4), anti-cardiolipin antibodies and possibly human immunodeficiency virus (HIV)-testing (Jayne, 2009). Miller and co-workers recommended anti-GBM antibodies (Miller et al., 2010). Other tests mentioned are serum albumin and calcium (Hunter et al., 2020).

Hardly any of the tests is specific for vasculitis. In systemic inflammation such as in LVV, marked elevations of ESR and CRP are common, as well as thrombocytosis and anemia (Weyand & Goronzy, 2014). Interestingly, in one study, 4% of patients with positive temporal arterial biopsy had normal ESR and CRP at diagnosis (Kermani et al., 2012). Positive serology for HBV may point to polyarteritis nodosa and positive serology for HCV for cryoglobulinemic vasculitis (Jennette et al., 2013). Low serum C4 is seen in cryoglobulinemic vasculitis (Ferri et al., 2004). A positive ANA may support the presence of an underlying systemic rheumatic disease such as systemic lupus erythematosus (SLE) (Monov et al., 2017). A few autoantibodies are helpful towards vasculitis diagnosis, such as ANCAs for AAV, anti-GBM for anti GBM-disease and anti-C1q antibodies for HUV (Csernok & Bossuyt, 2018).

ANCAs have a very important role in diagnosing vasculitis. Two types of ANCA assays are classically in use: the indirect immunofluorescence (IIF) or enzyme-linked immunosorbent assay (ELISA); the latter is the preferred method for AAV (Csernok, 2019). A negative PR3- and MPO-ANCA result does not eliminate the possibility of AAV. ANCA testing provides additional information for the final diagnosis but the diagnosis of AAV is based on the clinicopathological features of the patient (Csernok, 2019). ANCAs can be found in other diseases as well. Recently, an international consensus on ANCA testing beyond systemic vasculitis suggested testing ANCAs in anti-GBM disease and idiopathic interstitial pneumonia as well as in certain cases of other diseases (Moiseev et al., 2020).

2.3.2 Biopsy

Biopsy is often considered the gold standard of diagnostics. In vasculitides, biopsy of the involved tissue is essential, but not possible in all cases. For example, biopsy from the large arteries is usually not feasible and safe. Imaging is a crucial tool to localize the optimal biopsy site.

In LVV, the most common biopsy target is the temporal artery. The histological changes begin with a patchy inflammatory infiltrate, including giant cells, which may form granulomas in the vessel wall. Characteristic histopathologic findings

include panarteritis, often most clearly present in the media and composed of T lymphocytes and macrophages. Fragmentation of the internal elastic lamina and replacement with fibrous tissue is observed. Necrosis is usually not seen (Weyand & Goronzy, 2003). In GCA, meta-analysis showed an estimated diagnostic sensitivity of 77% for temporal artery biopsy (Rubenstein et al., 2020).

In MVV (PAN), typical histological findings include fibrinoid necrosis of the vessel wall with a chronic inflammatory infiltrate and luminal thrombosis. Lesions classically involve only part of the vessel circumference. All stages of activity from early to late coexist. The inflammatory process destroys the arterial wall leading to fibrosis and aneurysms. (De Virgilio et al., 2016; Miller et al., 2010)

In SVV, the vasculitic findings are typically seen in the capillary bed where histological changes include necrosis, fibrin deposition and leukocytoclasia (nuclear dust), and a mixture of neutrophils and lymphocytes. The most commonly affected organs are lungs, kidneys and skin (Miller et al., 2010; Miloslavsky et al., 2017). Deposition of immune complexes is seen in anti-GBM disease, IgAV, CV and HUV but not in AAV (Jennette et al., 2013). In GPA, the characteristic finding is necrotizing granulomatous vasculitis with a surrounding fibroblastic proliferation. Renal biopsy can be very useful for diagnosis and for estimating the prognosis of AAV. In renal biopsy, both in GPA and MPA, the pauci-immune, focal necrotizing glomerulonephritis, often with cellular crescents and glomerular thrombosis, is the most typical finding (Miller et al., 2010).

2.3.3 Imaging of vasculitis

There is an increasing availability and technical improvement of imaging techniques. This has had a deep impact in the evaluation of patients with suspected vasculitis, especially in those with LVV and to some degree in those with MVV. Magnetic resonance imaging (MRI), MR angiograms (MRA), computed tomography (CT), CT angiograms (CTA) and positron emission tomography (PET) may be used to detect arterial lesions. Ultrasound (US) is increasingly adopted to detect possible GCA. Conventional catheter-based angiography (digital subtraction angiography, DSA) is not commonly used but can be done in some situations, such as in assessing PAN or if endovascular intervention is needed (Guggenberger & Bley, 2020; Muratore et al., 2016).

Imaging methods may show morphological changes of vasculitis either directly by visualizing the vessel lesions or indirectly by demonstrating the effects of the vessel inflammation in the involved organ (Guggenberger & Bley, 2020). In different vasculitides, the radiologic appearance varies depending on the location, number, and size of the inflamed vessels. Usually, the vessel lesions themselves in SVV are below radiologic detection limits but indirect signs can be detected, e.g. soft tissue

damage in GPA (Guggenberger & Bley, 2020). Advantages and disadvantages of different imaging methods are depicted in *Table 2*.

This review concentrates on diagnostic imaging, not on monitoring vasculitis. In short, vascular imaging may aid in monitoring disease activity and may even have prognostic value, especially in LVV (Quinn & Grayson, 2019). However, routine follow-up examinations in LVV are not recommended by the European Alliance of Associations for Rheumatology (EULAR) since their clinical usefulness still needs to be defined (Dejaco et al., 2018). Performance (sensitivity and specificity) of different imaging modalities is showed in *Table 3.*

Table 2. Advantages and disadvantages of different imaging modalities (mainly concerning LVV).

IMAGE MODALITY	ADVANTAGES	DISADVANTAGES
Ultrasound	-inexpensive -widely available -comfortable for patient, fast -repeatable -high resolution (up to 0.1mm) -robust evidence in LVV	-limited view on thoracic and abdominal aorta -operator dependent
Computed tomograpghy angiography (CT/CTA)	-good overview on aorta and its branches -good availability -visualizes atherosclerotic plaques -fast	-radiation, approx. 8-16mSv -contrast agent unsuitable in kidney dysfunction
Magnetic resonance angiography (MR/MRA)	-excellent overview of involved arteries incl aorta -detailed view on vessel lumen and wall -cranial and extracranial arteries can be examined simultaneously -no radiation	-less sensitive than ultrasound and CT when detecting calcifications -long acquisition time -pricey -not suitable for pacemakers -cranial GCA diagnosis requires expertise
Positron emission tomography with CT	-excellent overview of involved arteries -shows early signs of inflammation -detects well infection and malignancy in diff diagnostics -variety of tracers to visualize different metabolic activities and mechanisms	-radiation approx. 8-10mSv -expensive and limited availability -difficulties to differentiate atherosclerosis from inflammation in femoral arteries -many potential tracers lack validation data

2.3.3.1 Ultrasound

Ultrasound imaging is easily accessible, economical, repeatable and does not expose patients to ionizing radiation. Ultrasound has no relevant side-effects (Schmidt, 2014a). The rheumatologists can perform the study themselves and the patient may receive the results during the examination. With modern ultrasound transducers, it is possible to acquire a resolution of 0.1mm, which is the highest among all imaging modalities in vasculitis (Schmidt, 2014b). Recently, EULAR has launched its recommendation concerning diagnosis and monitoring of LVV. They stated that "ultrasound should be the primary imaging test with suspected GCA presenting predominantly with cranial symptoms" (Dejaco et al., 2018). The major limitation of ultrasound imaging is that it does not visualize structures behind air or bone. Therefore, it provides scarce information about the thoracic aorta. Interpretation of ultrasound images is highly operator dependent. Sometimes it is difficult to differentiate arteriosclerosis from vasculitis. Typical arteriosclerosis is visible as irregular, eccentric and hyperechoic lesions (Muratore et al., 2016; Prieto-González et al., 2015).

Among the vasculitides, ultrasound is most comprehensively studied in LVV i.e. GCA and TAK (Schmidt, 2014b). Modern equipment with high frequency probes should be used (Dejaco et al., 2018). Vasculitis ultrasound examination consists of B-mode ultrasonography (gray scale) visualizing anatomy and Duplex ultrasound (combination of color Doppler and pulsed Doppler ultrasound) to depict data of blood flow and blood flow velocities (Schmidt, 2014a). The 'halo' sign, hypoechoic, non-compressible wall thickening of the artery caused by edema, is the main ultrasound finding in GCA (Dejaco et al., 2018). Measuring the thickness of the intima-media complex can help differentiate vasculitis from healthy arteries (Schäfer et al., 2017). Minimum screening should include temporal and axillary arteries (Dejaco et al., 2018; Muratore et al., 2016).

Imaging should be performed swiftly, ideally prior to therapy initiation. The classical ultrasound findings may disappear in few days with glucocorticoid therapy (Dejaco et al., 2018). Nowadays, the increasing number of fast-track clinics for rapid diagnosis should decrease disease complications, such as blindness (Diamantopoulos et al., 2016; Muratore et al., 2016).

2.3.3.2 Computed tomography

Computed tomography (CT) and CT angiography (CTA) are suitable to visualize inflammatory findings in deep, large arteries owing to the good spatial resolution and rapid scanning time. CTA can evaluate both the vessel lumen and wall of large arteries. CT can detect the aortic diameter and mural calcifications. (Pipitone et al., 2008). The major limitation of CT/CTA is the exposure to a significant amount of

ionizing radiation, which hinders its repeated use. Therefore, it is not the first choice of imaging in younger patients. Furthermore, CTA cannot be used in patients with renal insufficiency and in those allergic to iodine (Prieto-González et al., 2015).

In LVV, CTA can be used to diagnose early and advanced disease. In the early phase of LVV, CTA may show wall thickening with mural enhancement and a low-attenuation ring in the artery. In later phases of LVV, the vessel wall is marginally thickened with calcifications or high attenuation. As complications of inflammation, arterial stenosis, occlusion or calcifications may be seen (Pipitone et al., 2008; Prieto-González et al., 2015). In TAK, CTA has shown a significant number of cases with silent coronary involvement (Kang et al., 2014).

In PAN (one form of MVV), CT/CTA is often used to detect complications such as necrosis or bleedings in various organ systems. Depending on the vessel size, high-resolution CTA is able to discover the respective vessel lesions (Guggenberger & Bley, 2020).

In GPA and in other AAVs (forms of SVV), various lung manifestations such as inflammatory alveolar infiltrates and granulomatous changes are best visualized with CT (Guggenberger & Bley, 2020). Possible changes in osseous structures, e.g. in the cranial area, are also best revealed using CT (Guggenberger & Bley, 2020).

2.3.3.3 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a valuable method in the work-up of patients with superficial and deep large- to medium- sized vessel inflammation. MRI allows a high-resolution characterization of both the vessel wall and lumen (Ammirati et al., 2014). MRI is also suitable imaging modality for assessing affected soft tissue in the various vasculitides (Guggenberger & Bley, 2020). The advantage is that MRI does not use ionizing radiation and the gadolinium-based contrast medium is less nephrotoxic than iodinated contrast medium for patients with kidney disease. The main limitations of MRI are restricted availability, price, long acquisition time and rare adverse effects of contrast agents.

In LVV, the EULAR guidelines recommend high resolution MRI as an alternative investigation tool after ultrasound (Dejaco et al., 2018). Characteristic MRI findings in GCA consist of circumferential thickening and contrast enhancement of the arterial wall and narrowing of the vessel lumen (D'Souza et al., 2016). Presumably, contrast enhancement reflects active vascular inflammation (Dejaco et al., 2018). According to the EULAR guidelines, in patients with suspected TAK, MRI is the first imaging test to investigate the mural inflammation and/or luminal changes (Dejaco et al., 2018).

MRI is also useful in vasculitides other than LVV. In GPA, MRI can be used to show findings such as bone erosion, bone regeneration and mucosal swelling.

Contrast-enhanced MRI with MRA is the preferred modality in suspected CNS vasculitis (Pipitone et al., 2008).

2.3.3.4 Positron emission tomography

The combination of PET/CT is a useful diagnostic tool in the work-up of vasculitis. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is the most used tracer in vasculitis imaging (^{18}F-FDG-PET/CT) (Besson et al., 2011; Prieto-González et al., 2014; Puppo et al., 2014). FDG is a glucose analogue taken up by metabolically active cells with increased glucose consumption. Increased ^{18}F-FDG uptake in the vessel wall is the hallmark of vasculitis on PET (Fuchs et al., 2012). However, uptake is not specific for vasculitis since increased glucose metabolism is also seen in infections and malignancies (Besson et al., 2011). Moreover, uptake in organs with physiologically elevated glucose metabolism might limit the assessment of possible organ involvement in vasculitis. The advantage of ^{18}F-FDG-PET/CT is to establish a diagnosis of vasculitis in patients with constitutional, non-specific symptoms, and simultaneously search for an alternative diagnosis such as infection or malignancy (Ammirati et al., 2014). Also, the elevated metabolism in the vascular wall can be visualized before any structural anatomic changes have emerged (Slart et al., 2018). Traditionally PET is reported to visualize vessels over 4 mm diameter but not smaller vessels like renal arteries. More recently introduced clinical PET/CT cameras claim higher spatial resolution of 2 to 4mm (Janatuinen & Kemppainen, 2020). The temporal arteries are not visualized well due to the high physiological FDG uptake in the brain and limited resolution of the camera system (Slart et al., 2018). However, preliminary reports have shown that new generation ^{18}F-FDG-PET/CT is reliable also for examine cranial arteries (Nielsen et al., 2019; Sammel et al., 2019). The disadvantage of PET/CT is the exposure to radiation, cost and variable availability in different hospitals (Dejaco et al., 2018).

Concerning the vasculitides, most PET/CT research deals with LVV. The EULAR recommendation for imaging in LVV includes PET or PET/CT as one diagnostic method, stating that PET "may be used for detection of mural and/or luminal changes in extracranial arteries to support diagnosis of LV-GCA" (Dejaco et al., 2018). This means that in cranial GCA other methods, such as ultrasound, are higher in hierarchy. In 2018, nuclear medicine interest committees released a joint procedural recommendation on ^{18}F-FDG-PET/CTA imaging, including data acquisition and interpretation in LVV and polymyalgia rheumatica (Slart et al., 2018). There are different grading methods to assess vascular activity (Puppo et al., 2014; Slart et al., 2018). When using a visual qualitative method, higher tracer uptake in the vessel wall than in the liver is suggestive of vasculitis, especially in LVV (Puppo et al., 2014). Characteristic vascular inflammation of LVV appears in the

aorta and its main branches as linear or segmental pattern of FDG uptake (Besson et al., 2011). PET/CT has proven to be useful in the diagnosis of TAK (Farrah et al., 2019). Ideally, PET imaging should be performed before initiation of glucocorticoid treatment or within few days from the start, since the diagnostic accuracy dramatically declines with treatment (Imfeld et al., 2017; Nielsen et al., 2018).

There is scarce data about how ^{18}F-FDG-PET/CT visualizes different vasculitides other than LVV. Some reports show that PET may be useful in detecting small-vessel vasculitis (Kemna et al., 2015; Soussan et al., 2014). In some cases of SVV, PET/CT might reveal distinct imaging findings in small- and medium-sized arteries showing a tree-root-like uptake pattern (Salomäki et al., 2014). In addition, recognition of specific distribution patterns of FDG uptake may contribute to the diagnosis of concurrent PMR in addition to LVV (Yuge et al., 2018).

Table 3. Performance of different imaging modalities in large vessel vasculitis.

Imaging modality	Author	Reference standard	Type of study	N (pt.)	Sensitivity (95%CI)	Specificity (95%CI)
Ultrasound (GCA)	Duftner et al., 2018	Clinical diagnosis	Meta-analysis	605	77% (62–87)	95% (85–99)
CTA	Lariviere et al., 2016	Clinical diagnosis	Prospective study	24	73% (45–92)	78% (40–97)
MRA	Duftner et al., 2018	Clinical diagnosis	Meta-analysis	509	73% (57–85)	88% (81–92)
		TAB		443	93% (89–96)	81% (73–87)
PET or PET/CT	Lee et al., 2016	ACR 1990 classification criteria	Meta-analysis	170	76% (69–82) *	93% (89–96)*

*Lee et al study includes both GCA and TAK patients. When GCA is analyzed alone, the reported sensitivity is higher, in average 83% (72–91). CI: confidence interval; CTA: computed tomography angiography; GCA: giant cell arteritis; MRA: magnetic resonance angiography; PET: positron emission tomography.

2.4 Diagnostic delay and pitfalls in vasculitis diagnosis

2.4.1 Diagnostic delay in different vasculitides

Vasculitis is a difficult diagnosis, which may be associated with significant diagnostic delay. Delay may arise if patients are not aware of the often non-specific symptoms (patient's delay) or health care providers do not recognize the disease (doctor's delay). Different studies report great variability in diagnostic delay. Among vasculitides, the data concerning the diagnostic delays is scarce.

In recent years, most published studies focusing on the diagnostic delay are about GCA. The reason for this interest has been the development of new fast-track clinics, which have shortened the diagnostic delay (Diamantopoulos et al., 2016; Patil et al., 2015). In 2017, Prior and co-workers published a large systematic review and meta-analysis on the diagnostic delay of GCA (Prior et al., 2017). They also examined the role of GCA-specific characteristics for delay. Sixteen articles provided data for meta-analysis. Prior and the group reported that the mean diagnostic delay was 9.0 weeks (95% CI, 6.5–11.5 weeks) between symptom onset and GCA diagnosis. Patients with cranial features of GCA (e.g., headache, scalp tenderness) were diagnosed significantly faster than patients with non-cranial symptoms (constitutional symptoms such as fever, polymyalgia), 7.7 (2.7–12.8) weeks vs 17.6 (9.7–25.5) weeks, respectively (Prior et al., 2017). In line with Prior et al., Monti et al. reported in their systemic literature review that patients with LV-GCA are more likely to have a longer diagnostic delay and tend to be younger and more likely female than other GCA patients (Monti et al., 2019). In 2015, Patil et al. reported results from one of the first fast-track clinics. They examined 135 consecutive patients and reported a reduction of time from symptom onset to diagnosis as well as significant reduction (from 37% to 9%) in irreversible sight loss (Patil et al., 2015). The other type of LVV, TAK, has been less studied. Experts have reported a significant delay ranging from months to years (Kim & Beckman, 2018; Mason, 2010).

In Kawasaki disease (KD), the diagnostic delay seems shorter than in LVV. Minich et al. reported that in KD diagnostic delay was 7.9 ± 3.9 days (Minich et al., 2007). Delayed diagnosis is more frequent in older children with KD and they are reported to have a higher prevalence of coronary artery abnormalities (McCrindle et al., 2017). For another MVV, PAN, only one recent study is available and the diagnostic delay was mean 24 ± 42 months (Sreih et al., 2021).

For GPA, a form of AAV, a Finnish cohort (n=489) from 1981-2000 showed a diagnostic delay ranging from 17 months to 4 months shortening, towards the end of the observation period due to improved awareness and diagnostic methods (Takala

et al., 2008). A more recent AAV cohort study (n=130) from England between 2013 and 2014 reported a diagnostic delay ranging from 0 to 53 days with a median of 6 days for inpatients and a median of 2.6 months from symptoms to diagnosis (Pearce, McGrath, et al., 2018). A literature search provided only one study reporting delays for MPA (mean 32±57 months, n=53 patients) and EGPA (mean 60±100 months, n=58 patients) (Sreih et al., 2021). Little is known about the diagnostic delay in IgAV, but it is likely less than in many other vasculitides with a median of 7 days has been reported (Hočevar et al., 2019; Sreih et al., 2021). A literature search did not provide studies on diagnostic delays of other immune complex SVV.

In Behçet's disease, a type of VVV, a large multicenter study of 661 patients reported the mean duration between the onset symptom and the fulfilment of diagnostic criteria to be 4.3 ± 5.7 years (Alpsoy et al., 2007). Regarding Cogan's syndrome, there are only a few hundred cases reported in the literature. One study of 32 patients reported a mean delay of 21.9 months (10 months for typical Cogan's syndrome and 34.6 months for atypical Cogan's syndrome) (Grasland et al., 2004).

2.4.2 Differential diagnosis of vasculitis – mimics and secondary causes of vasculitis

The clinical suspicion of vasculitis is the key to diagnosis. Concurrently, a fundamental feature of the work-up is the exclusion of mimics and secondary causes of vasculitis as the symptoms and findings resemble each other (Jayne, 2009; Pettersson & Konttinen, 2005). Vasculitis mimics (or pseudovasculitis or vasculitis-like syndromes) represent a heterogeneous group of disorders and can be characterized more as vasculopathy rather than as true vasculitis (Miloslavsky et al., 2015). Vasculitis mimics are not rare diseases and they should be kept in mind during the work-up for vasculitis diagnosis (Maningding & Kermani, 2021; Pettersson & Konttinen, 2005). Secondary vasculitis is an inflammatory vasculitis where the underlying etiology or trigger can be identified. Sometimes it is hard to separate secondary vasculitis from some primary vasculitides which are known to be related to infections (such as polyarteritis nodosa and HBV or cryoglobulinemic vasculitis and HCV). Malignancies can be both mimics and secondary causes of vasculitis. Paraneoplastic vasculitis is covered in more detail in chapter *2.4.2.2.*

Among the most important diseases to exclude are infections and malignancies (Jayne, 2009; Pettersson & Konttinen, 2005). The immunosuppressive therapy used for vasculitis could worsen these conditions and lead to harmful consequences. However, sometimes even a meticulous work-up for vasculitis diagnosis may leave some uncertainty regarding the exact diagnosis. The potential for confusion may be caused e.g. by the presence of ANCA in some patients with infective endocarditis or cholesterol emboli (Moiseev et al., 2020). The clinical presentation of vasculitis is

broad, which makes the differential diagnostics challenging; a detailed discussion of potential mimics and secondary causes is beyond the scope of this review. *Table 4* summarizes various causes of vasculitis mimics and secondary causes. Drug-induced vasculitis is covered in more detail in a separate chapter.

Table 4. Mimics and secondary causes of vasculitis.

MIMICS OF VASCULITIS	SECONDARY CAUSES OF VASCULITIS	
Atheroembolic disease	**Infections**	Tuberculosis
Atheromatous vascular disease		Hepatitis B
Anti-phospholipid syndrome		Hepatitis C
Multiple myeloma		HIV
Infective endocarditis		Parvovirus
Other chronic infection		
Paraneoplastic syndromes	**Malignancy**	Lymphoma
Genetic vascular disorders (e.g., Marfan's, Ehlers-Danlos)		Solid organ malignancy
Autoinflammatory syndromes	**Connective tissue disorders**	Rheumatoid arthritis
Hypersensitivity reactions		Systemic lupus erythematosus
Cocaine and amphetamine abuse (levamisole-induced)		Scleroderma
Calciphylaxis		Sjogren's syndrome
IgG4-related disease (small vessels)	**Drugs**	Penicillamine
		Propylthiouracil
		Hydralazine
		Minocycline
		Cocaine
	Environmental expose	Dust, silica
	Other	IgG4-related disease (aortitis)

Adapted from Jayne (Jayne, 2009) and Miloslavsky (Miloslavsky et al., 2015).

2.4.2.1 Drug-induced vasculitis

Drug-induced vasculitis is an inflammation of blood vessels caused by using diverse pharmaceutical agents and is considered secondary vasculitis. The most common symptom is cutaneous vasculitis which may be accompanied by arthralgia, myalgia and skin rash (Holder et al., 2002). Vasculitis usually involves small vessels,

primarily capillaries, venules, and arterioles. The presentation may be similar to small-vessel disease such as ANCA-related vasculitis, or medium-sized vessel vasculitis like polyarteritis nodosa (Grau, 2015). Large-vessel presentation is rare. However, there are some case reports, where LVV is suspected as an adverse drug reaction to granulocyte colony-stimulating factor (G-CSF) (Lardieri et al., 2018; Parodis et al., 2019). G-CSF is a myeloid growth factor indicated to reduce neutropenia. Since the first drug filgrastim was approved in 1991, G-CSF has helped to revolutionize cytotoxic chemotherapy by preventing neutropenic infections. The usage has increased within the past two decades after the introduction of long-acting PEGylated G-CSFs and more inexpensive biosimilar G-CSF drugs (Bendall & Bradstock, 2014). This class of drugs is usually considered well-tolerated and safe.

The pathogenesis of drug-induced vasculitis is not well understood. It is likely multifactorial, requiring an environmental trigger which leads to self-reactivity in a person with genetic predisposition (Grau, 2015). The interval between the first exposure to a drug and the appearance of symptoms is reported to be extremely variable (hours to years) (Holder et al., 2002). Some of the common drugs associated with drug-induced vasculitis are listed in *Table 4* above. There is emerging data that monoclonal antibodies, such as rituximab and tumor necrosis factor alpha blockers, are associated with drug-induced vasculitis (Grau, 2015). For diagnosis, biopsy of affected tissue is important as well as suitable vascular imaging. In early disease, rapid cessation of the offending drug leads to full recovery, while in a more advanced disorder the use of immunosuppressive therapy may be necessary (Grau, 2015).

2.4.2.2 Paraneoplastic vasculitis

Paraneoplastic syndromes consist of diseases or manifestations that are not caused directly by the tumor or by its metastases. Instead, they are mediated by soluble factors, such as cytokines and hormones, secreted from a tumor or are a consequence of immune mechanisms directed against tumor cells. They take place in areas remote from the underlying malignancy (Manger & Schett, 2014). A variety of rheumatic manifestations can be associated with malignancies such as cancer-associated myositis, paraneoplastic polyarthritis, hypertrophic osteoarthropathy and RS3PE (remitting seronegative symmetrical synovitis and pitting edema) (Manger & Schett, 2018). In true paraneoplastic syndrome, removal of the malignancy will result in fast regression of all symptoms, thus providing proof of the paraneoplastic nature of a condition (Manger & Schett, 2014).

Paraneoplastic systemic vasculitis is probably not very common (Manger & Schett, 2018) and sometimes it is difficult to evaluate whether there is a paraneoplastic or secondary disease. Systemic necrotizing vasculitis has been reported in association with hairy cell leukemia. Polyarteritis nodosa has been

associated with solid tumors and hematological malignancies (Fain et al., 2007; Solans-Laqué et al., 2008). A few cases of GCA have been described in patients with various, mostly haematological malignancies (Park et al., 2011; Solans-Laqué et al., 2008) and one case secondary to a pulmonary neuroendocrine tumor (Aguiar & Vincent, 2015). Skin limited vasculitis is more common than systemic disease. Fain et al. described a series of sixty vasculitis patients with associated malignancy and among these, cutaneous leukocytoclastic vasculitis was the most common form of vasculitis seen in 45% of the patients (Fain et al., 2007).

2.5 Overview of the management of vasculitis

The treatment of vasculitis consists of rapid induction of remission followed by maintenance therapy. The intensity of the treatment depends on the severity of the vasculitic manifestations. Balancing is needed between the potential target organ damage caused by the disease and drug toxicity from therapy. In most cases, a glucocorticoid is the principal first-line drug. Glucocorticoids are effective, but adverse effects are common in a high proportion of patients.

In vasculitides affecting large vessels (GCA and TAK), high-dose systemic glucocorticoids, often prednisolone, are the mainstay of therapy and should be instituted promptly once the diagnosis of LVV is strongly suspected (Agueda et al., 2019; Buttgereit et al., 2016; Zaldivar Villon et al., 2019). TAK has a chronic and relapsing course of the disease, so immunosuppressive glucocorticoid-sparing agent is often immediately started in combination with the glucocorticoid. In GCA, an immunosuppressive “steroid-sparing” agent is usually started if relapse occurs or if there is a high risk for an adverse event caused by the glucocorticoid. Methotrexate is the most common traditional immunosuppressive medication in both GCA and TAK; alternative treatments include azathioprine, leflunomide and mycophenolate (in TAK) (Agueda et al., 2019; Hellmich et al., 2020; Zaldivar Villon et al., 2019). Tocilizumab, an IL-6 receptor antagonist, has proven to be effective in GCA (Stone et al., 2017). The 2018 update of the EULAR recommendations for the management of LVV and the guidelines of the British Society of Rheumatology suggest starting tocilizumab in patients with CGA with refractory or relapsing disease or as initial therapy in patients at risk of glucocorticoid-related adverse events (Hellmich et al., 2020; MacKie et al., 2020). In TAK, selected cases with refractory or relapsing disease may benefit from adding a TNF inhibitor to the initial therapy. Vascular intervention may be needed but preferably it should be done during stable remission (Hellmich et al., 2020).

In vasculitides affecting medium-sized vessels (KD and PAN), treatments differ from one another. In KD, the main treatment is intravenous immunoglobulin (IVIG), which is targeted at preventing the development of coronary artery aneurysm.

Unfortunately, about 15% of patients do not respond to IVIG and these children need further anti-inflammatory treatment such as glucocorticoids. Aspirin is recommended during the acute phase of disease (Dietz et al., 2017; Rowley & Shulman, 2010). In PAN, glucocorticoids and cyclophosphamide are the principal therapies. The distribution of the affected organs and disease progression determine the intensity of therapy (De Virgilio et al., 2016). In mild cases of PAN, glucocorticoids can be used as monotherapy. In the presence of critical organ involvement, cyclophosphamide in combination with glucocorticoid is needed to induce remission and afterwards treatment can be continued with a less toxic immunosuppressant such as methotrexate or azathioprine (De Virgilio et al., 2016; Mukhtyar et al., 2009; Ozen, 2017). In refractory disease, rituximab may be considered. HBV-associated PAN often requires treatment with an antiviral agent for the control of the infection. For cutaneous PAN, less aggressive therapy centered on non-steroidal anti-inflammatory drugs is a recommended strategy (De Virgilio et al., 2016; Mukhtyar et al., 2009).

In vasculitides involving mainly small vessels, the treatment strategies of AAV and immune complex SVVs are different. The clinical spectrum of the AAV is broad ranging from a skin rash to fulminant multisystem disease. Treatment should be adjusted to the severity of the disease. Management of induction and maintenance of remission are similar in GPA and MPA; EGPA has some differences in approaches to management (Wallace & Miloslavsky, 2020; Yates & Watts, 2017). In GPA and MPA, for induction of remission, high dose glucocorticoids by intravenous or oral route plus either rituximab or cyclophosphamide are usually used. In certain cases of severe disease, plasma exchange may be used. For maintenance therapy, there is accumulating evidence that rituximab is the first choice of therapy. Azathioprine, methotrexate and mycophenolate are alternatives and may be preferred as first choice depending on the patient-related factors (Guillevin et al., 2014; Wallace & Miloslavsky, 2020; Yates et al., 2016). Regarding EGPA, most patients achieve remission with glucocorticoid monotherapy. In severe cases, cyclophosphamide is added to the glucocorticoid for remission induction. Additional immunosuppressants are used to maintain remission if needed. (Yates et al., 2016; Yates & Watts, 2017). Mepolizumab, an anti-IL-5-antibody, has proven to be effective in EGPA (Wechsler et al., 2017). Avacopan, a C5a receptor inhibitor, is a new promising therapeutic choice for AAV (Jayne et al., 2021).

Immune complex vasculitides include IgAV, CV, anti-GBM disease and HUV. In children, IgAV often resolves spontaneously but in adulthood the disease may be more severe. Non-steroidal anti-inflammatory drugs are used to relieve pain symptoms. Prednisolone (or intravenous methylprednisolone) may be used in severe gastrointestinal or joint symptoms; however, evidence for treatment is limited. In cases with renal involvement (impaired renal function or marked proteinuria), a

glucocorticoid, azathioprine, mycophenolate, or cyclophosphamide may be used. In small studies, rituximab has been shown to be efficient (Hernández-Rodríguez et al., 2020). For patients with CV, treatment is linked closely to the underlying disorder. For patients with HCV-associated CV, treatment should be concentrated on the use of antiviral therapy. In severe cases, cyclophosphamide or rituximab may be used. Plasmapheresis can be used as additional therapy to rituximab and/or antiviral therapy. The role of glucocorticoid is not defined; however, they are being used (Baerlecken & Schmidt, 2013; Goglin, S., Chung, 2016; Montero et al., 2018). Anti-GBM disease usually progresses to end-stage renal disease if left untreated. For most patients, plasmapheresis is recommended in combination with immunosuppressive therapy. As a first-line immunosuppressive therapy, glucocorticoids and cyclophosphamide are given in combination. If cyclophosphamide cannot be administered, rituximab or mycophenolate may be considered (Gulati & McAdoo, 2018; McAdoo & Pusey, 2017). Treatment of HUV is based on the clinical presentation and the severity of the disease. However, published data on the management of HUV are scarce. The cornerstone of treatment is glucocorticoids which may be combined with dapsone, colchicine or hydroxychloroquine in mild or moderate disease. In more severe disease, other agents such as mycophenolate, methotrexate, azathioprine, and cyclophosphamide are being used based on some reports. Biological agents, such as rituximab, may be beneficial in relapsing or severe disease. (Bulva & Simon, 2017; Jachiet et al., 2015).

In BD, growing evidence supports the different clinical phenotypes can be distinguished. Therapeutic approach could be directed on the patient's phenotype. Treatment options include colchicine and glucocorticoids in mild disease and a wide-range of immunosuppressive agents in more advanced cases (Bettiol et al., 2019). In Cogan's syndrome glucocorticoids are the first-line therapy, other immunosuppressives can be used as well (Durtette et al., 2017).

2.5.1 The effect of glucocorticoid therapy on the diagnostic accuracy of biopsy and imaging

Glucocorticoids are the first-line immunosuppressive agents when vasculitis is strongly suspected. In cases with severe symptoms, therapy must be started even if the diagnosis is uncertain, and the diagnostic work-up continues along with glucocorticoid therapy. Unfortunately, the use of immunosuppressive medication reduces the diagnostic value of imaging and biopsy. This review focuses how glucocorticoid therapy effects the diagnostic accuracy. Other immunosuppressants, such as tocilizumab, might have different effects on biopsy and imaging findings but so far the data are scarce (Camellino et al., 2020).

Histopathological examination of a tissue biopsy is useful in confirming the diagnosis in relation to the clinical findings. Biopsy is considered gold standard in certain vasculitides, such as temporal artery biopsy (TAB) in GCA. However, a negative biopsy does not exclude GCA. A negative result can be caused e.g., by the presence of skip lesions, wrong biopsy site or healed inflammation. In GCA, resolution of the inflammatory infiltrate occurs slowly, and histopathologic evidence of vasculitis may be seen as long as one month after glucocorticoid therapy (Narváez et al., 2007). Inflammatory changes can be persistent, too. Maleszewski et al. studied 40 biopsy proven GCA-patients with a second TAB, which was taken 3-12 months after the first diagnostic TAB was obtained. Patients were in clinical remission and on glucocorticoid treatment. However, 24 out of 40 second biopsy samples showed unequivocal findings of vasculitis (Maleszewski et al., 2017). The significance of this finding is unclear, but the explanation could be that acute inflammation is followed by persistent myointimal proliferation (Camellino et al., 2020). In other vasculitides, such as AAV, there is no reliable data to determine how rapidly glucocorticoids affect the histological changes.

Different imaging techniques show different aspects of inflammation; hence glucocorticoid treatment has ambiguous effects depending on the modality. When examining GCA with ultrasound, the 'halo' sign of the temporal arteries diminishes within 1–4 weeks after glucocorticoid initiation (Dejaco et al., 2018; Van Der Geest et al., 2019). Wall thickening in larger arteries, e.g., axillary arteries, may persist for months (Schmidt, 2018). When using ^{18}F-FDG-PET/CT, arterial uptake decreases after initiation of glucocorticoid treatment. Based on the literature, the diagnostic accuracy diminishes significantly somewhere between three and ten days on glucocorticoids (Imfeld et al., 2017; Nielsen et al., 2018). However, despite apparent clinical remission, many PET scans show persistent arterial uptake, which may reflect vascular remodelling and chronic changes (Blockmans et al., 2006; Hellmich et al., 2020). Concerning CT/CTA and MRI/MRA it is known that active contrast enhancement changes resolve during treatment (Camellino et al., 2020; Farrah et al., 2019). The diagnostic sensitivity of MRI has been noted to diminish as early as after five days in both cranial- and LV-GCA (Adler et al., 2017; Klink et al., 2014). Most studies of CT and MRI are follow-up studies where control imaging was performed many weeks to months after the initial imaging. Persistent signs of vasculitis, such as wall thickening, are seen in both modalities (Prieto-González et al., 2015). In other vasculitides, the effect of glucocorticoids on imaging findings is virtually unexplored.

2.6 Economic burden of vasculitis to the healthcare system

There is lack of data about the economic burden of systemic vasculitis especially on different healthcare systems. The Finnish healthcare system covers the whole population and is mainly produced by the public sector and funded through general taxation.

2.6.1 Costs of vasculitis

In 2012, a systemic literature review on this subject failed because of a paucity of relevant papers. Trieste et al. aimed to search the literature of the last decade in order to evaluate the economic and societal impact of systemic vasculitis (Trieste et al., 2012). They found only three articles that fulfilled the criteria (Krulichova et al., 2004; Reinhold-Keller et al., 2002; Sut et al., 2007) and concluded "the few studies assessing direct costs suggest that systemic vasculitides determine high costs related to their severity, the need for hospitalization and costly procedures". Regarding all systemic vasculitides, in 2018 Thorpe et al. published a retrospective report using the US Medicare medical claims from 2010. They analyzed 176,498 patients with ≥ 1 claim including the diagnosis of systemic vasculitis and 46,561 non-systemic vasculitis beneficiaries. As a result, Medicare spent annually $11,004 more per patient on medical services with systemic vasculitis patients. This is double the annual healthcare expenditures compared with their non-vasculitic counterparts (Thorpe et al., 2018).

Regarding GCA, a study from the U.S. by Babigumira et al. reported that patients with a recent GCA diagnosis (n=1293) had significantly higher health care costs compared with the patients without GCA and, after multivariate adjustment, the difference in the first years' cost was over $16,400 (Babigumira et al., 2017). In 2017, a French population-based, retrospective study assessed the costs of GCA during a 5-year period of 96 GCA patients and for 563 matched controls. In this study, Mounié et al. showed that the cumulative incremental cost during the first 3 years of GCA exceeded €6,400 compared with matched controls, representing an adjusted increase of 72% in costs. The main incremental cost drivers were paramedical procedures, in-patient stays, medication and medical procedures (Mounié et al., 2018). Mounié et al. and Babigumira et al. received very distinct results within the first year, €2,840 versus $16,431, respectively. Mounié et al. speculated that the difference is partly explained by the societal perspective and the differences in health care systems (Mounié et al., 2018). In 2019, Valent et al. examined the healthcare burden and cost of illness (COI) of GCA in Italy (Valent et al., 2019). The GCA patients (n=208) were retrospectively identified from the databases from 2001to 2017. The overall estimated direct healthcare cost was €2374

per patient year within an observation time of 4.5±3.6 years. Costs were largely determined by the costs for hospitalizations (70%) and medications (27.5%). For comparison, the health care cost of GCA was similar to that estimated for diabetes in the same area (Valent et al., 2019). Interestingly, in 2019 Mounié et al. reported that GCA patients (n=100) with polymyalgia rheumatica symptoms (n=54 out of 100) had a cumulative additional cost due to polymyalgia rheumatica of €8,801 during the first three years of follow-up (Mounié et al., 2019).

Regarding other vasculitides than GCA, most published data consider AAV as an entity or subgroups of EGPA, GPA and MPA separately. Recently, an Italian group characterized the economic burden and direct COI of AAV (Quartuccio et al., 2020). Within an 8-year follow-up, the overall healthcare costs were € 6,168 per patient-year which is more than two times higher than that of patients with GCA in the same region (Valent et al., 2019). ANCA-positive patients showed much higher costs than ANCA-negative. Mortality and hospitalization rates were both significantly related to the presence of ANCA in this study (Quartuccio et al., 2020). In GPA, a U.S. study from 2020 examined inpatient resource utilization and showed that total hospitalization costs were on average $17,000 higher per admission than in non-GPA patients (Ungprasert et al., 2020). Regarding the costs of adult IgAV or other systemic vasculitides, there are no reliable studies.

2.6.2 Factors associated with high costs during the diagnostic period

The vasculitides are rare disease and there is scarce information about the main cost drivers during the diagnostic phase. To reduce the diagnostic costs, it would be essential to understand more about the individual cost drivers. As summarized in 2.6.1, particularly the disease severity and hospitalization increase the overall costs. Acute renal replacement therapy increases the costs significantly (Srisawat et al., 2010). High use of outpatient physician, laboratory, and radiology visits, and ophthalmologic procedures were reported for the first 6 months after diagnosis, thus increasing the costs (Koster et al., 2017; Valent et al., 2019). Use of medications cause additional costs (Babigumira et al., 2017; Thorpe et al., 2018), but their impact on the expenses during the diagnostic period in unknown.

3 Aims

1. To evaluate the impact of using ^{18}F-FDG-PET/CT for diagnosing systemic vasculitis in a real-life cohort of patients. Because glucocorticoids are known to interfere with the accuracy of ^{18}F-FDG-PET/CT, we aimed to observe the effect of glucocorticoid treatment on the performance of ^{18}F-FDG-PET/CT imaging.
2. To explore the relation between LVV, G-CSF and chemotherapy among breast cancer patients via a systemic literature review. To describe six new patient cases with probable G-CSF and breast cancer chemotherapy induced LVV.
3. To investigate the diagnostic delay in systemic vasculitis, the total costs during the diagnostic period and first year of care, and to examine how the diagnostic delay affects the costs in a tertiary health care center. A secondary aim was to evaluate how PET/CT affects the costs of diagnostics.

4 Materials and Methods

4.1 Study populations

4.1.1 Study I

The cohort consisted of consecutive patients with suspected systemic vasculitis encountered between May 2011 and June 2015. Patients were prospectively enrolled in Turku University Hospital, Turku, Finland. This study population was part of the Positron Emission Tomography of Infection and Vasculitis (PETU) study (clinical trial number: NCT01878721).

4.1.1.1 Evaluation of the diagnoses and diagnostic cohorts

In order to establish the final diagnosis, we required a minimum of six months of follow-up. The diagnoses were confirmed by consensus-based decisions made by specialists after evaluation of the clinical picture, extensive routine workup, imaging findings including ^{18}F-FDG-PET/CT scan and histology. For further analyses, vasculitis patients were divided into four clinically relevant groups based on the diagnosis: LVV, medium- and small-vessel vasculitis, unspecified vasculitis, and ANCA-associated vasculitis (AAV). The AAV group included six patients with the diagnosis of either GPA, EGPA or MPA. In this group, 5 patients were ANCA-positive, and the remaining patient had histological confirmation of vasculitis. The ACR 1990 classification criteria for vasculitis were used to evaluate this whole vasculitis cohort (Fries et al., 1990; Hunder et al., 1990).

4.1.2 Study II

In study II the inclusion criteria for the patient cases and for the literature review cases were the following: "(1) a patient with malignancy, who had received chemotherapy or G-CSF and (2) was diagnosed with new LVV within 12 months after initiation of new chemotherapy or G-CSF." Excluded were the patients with unclear temporal relationship between the drug and LVV, other probable cause than a drug behind LVV, insufficient data or a diagnosis other than LVV. In this

study, carotid artery inflammation, which can be described also as carotidynia or transient perivascular inflammation of the carotid artery (TIPIC), was included in the LVV group, as the clinical picture and imaging findings are compatible with LVV.

The six patients in our case series were identified between 2016 and 2018 at the departments of Rheumatology at Turku University Hospital (three cases) and Helsinki University Hospital (three cases), Finland. These rare cases were enrolled consecutively as they were encountered in the clinics. All patients had a minimum of six months of clinical follow-up and a follow-up imaging of vasculitis. The extent and modality of imaging was based on the attending physician's decision. Most patients had imaging performed with multiple modalities.

4.1.3 Study III

The patient population of study III consisted of patients over 16 years with a new diagnosis of systemic vasculitis made between January 2010 and November 2018. Searched ICD-10 codes were D69.0, D89.1, L95.0, L95.8, L95.9, M30.0, M30.1, M30.8, M31.0, M31.3, M31.4, M31.5, M31.6, M31.7, M31.8, M31.9, M35.2. All patients needed hospitalization. The patients were retrospectively identified from the medical records of Turku University Hospital with the help from the center for clinical informatics (Auria Clinical Informatics). We required that the diagnosis code for systemic vasculitis was entered minimum three times. Furthermore, two experienced rheumatologists validated each patient's diagnosis based on the ACR vasculitis criteria and/or the clinical presentation of the disease. Patients excluded from the study had an uncertain or a false vasculitis diagnosis, a previous diagnosis of vasculitis, concurrent or metastatic malignancy or paraneoplastic vasculitis, a final diagnosis of anti-GBM disease, another disease causing significant costs or technical issues. 450 eligible patients were identified of which 317 fulfilled the criteria and were included in the study.

4.2 PET/CT imaging (study I)

PET/CT imaging was performed at Turku PET Center when vasculitis was suspected on clinical grounds. After fasting for a minimum of ten hours, patients had a vertex-to-toes ^{18}F-FDG-PET/CT scan (64-slice Discovery VCT, General Electric Medical Systems, Milwaukee, WI, USA). The mean injected ^{18}F-FDG dose was approximately 270 MBq. After a mean injection-to-scan time of 57 minutes (range= 44–79 minutes), a whole-body PET acquisition was performed following low-dose CT (kV 120, Smart mA range 10-80). A group of patients also underwent a diagnostic high-dose contrast-enhanced CT (CECT) scan (kV 120, Smart mA range

100–440) during the arterial phase after an injection of contrast agent. Of all 82 patients, 21 patients underwent an ^{18}F-FDG-PET/CECT scan and 61 patients underwent an ^{18}F-FDG-PET/CT scan. The need for CECT was based on the clinician's and/or nuclear medicine physician's decision.

Blood glucose levels were below 10 mmol/L in all patients. PET images were reconstructed in 128 × 128 matrix size in full 3D mode using maximum-likelihood reconstruction with an ordered-subsets expectation maximization algorithm (VUE Point, GE Healthcare). An experienced nuclear medicine physician, blinded to clinical findings, performed the visual analysis of the images. For consensus-based diagnosis, re-evaluation was done by the research team. Vasculitis was diagnosed by ^{18}F-FDG-PET/CT when a linear uptake pattern was found in the large arterial walls and/or its branches with an intensity equal or above the liver. Vasculitis in small-to medium-sized vessels was considered, when the activity was higher than the vascular background activity and showed a tree-root-like uptake pattern as previously described by Salomäki et al.,2014.

Assessment of CECT data was carried out by a radiologist, who was blinded for the diagnosis and treatment regimens. Eight arterial segments (i.e., temporal, carotid, subclavian, axillary, aortic, femoral, renal, celiac) were evaluated for the presence of anatomical findings suggesting vasculitis by using a 4-point ranking scale as follows: 0=negative, 1=positive, 2=equivocal and 3=not visualised.

4.3 Systematic literature review (study II)

A systematic literature review was performed following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Page et al., 2021). Three authors conducted two separate systematic literature searches in MEDLINE via PubMed. The first search focused on finding reports and articles about cancer patients receiving chemotherapy or G-CSF or both prior to the onset of new LVV. Comprehensive search terms for breast cancer, chemotherapy and LVV were used. We focused on breast cancer, but other malignancies were not excluded if they showed up in the search. The second systematic literature search was specifically focused on assessing the connection between G-CSF and LVV by using comprehensive keywords for those. The results of these searches were fused by using the PRISMA flow chart system. Retrieved and relevant papers were manually searched for additional references. In this search, no new essential articles emerged.

4.4 Defining the diagnostic period and costs in tertiary-health care (study III)

4.4.1 Diagnostic period and one-year period

The medical records were manually searched to find the first contact with the tertiary-health care concerning the suspicion of new vasculitis. This was identified as 'the first date'. In addition, we manually searched the exact date when the vasculitis diagnosis was recorded in the medical files, and this was considered as 'the diagnosis date'. The diagnostic period (or diagnostic delay) was defined as the time interval between the first date and the diagnosis date. For each patient, we assessed data during the diagnostic period and within one year after the first date defined as 'one-year period'

4.4.2 Diagnostic examinations and costs

Auria Clinical Informatics searched the hospital records for the following data during the diagnostic period and one-year period: the number and costs of inpatient diagnostic examinations, the days and costs of hospitalization and the total costs. The costs were caused by multiple components and included the following: a) diagnostic procedures such as laboratory, radiology, and pathology examinations b) hospitalization c) medical therapy during hospitalization and d) outpatient visits related to the vasculitis. Total costs also included other expenses such as endoscopies or biopsies related to the diagnostic process. The staff services, surroundings and the equipment were included in the costs. To reliably analyze the costs originating from management of vasculitis, we have excluded the possible confounding cost of the departments which are not likely connected to the vasculitis disease. Those departments are the following: anesthesiology, clinical genetics, dental care, hematology, neurosurgery, obstetrics and gynecology, psychiatry, occupational health, oncology, orthopedics, pain clinic, physical medicine, rehabilitation, thoracic surgery, and traumatology. For the same reason, the costs from physiotherapy, speech therapy, occupational therapy or nutritional therapy were not collected. Costs were recorded and reported as true costs, which were charged from the final payer. All costs were in euros. The charges for the patient were only nominal for both the hospitalization and the outpatient visits. The fee was equal for all patients despite the treatment received.

4.4.3 Grouping of diagnoses

In order to perform statistical calculations, the diagnoses were grouped into three clinically relevant groups: IgAV and other small-vessel vasculitis (ICD-10 codes

D69.0, D69.2, D89.1, L95.0, L95.8, L95.9), AAV (ICD-10 codes M30.0, M30.1, M30.8, M31.0, M31.3, M31.7, M31.8, M31.9) and LVV (ICD-10 codes M31.4, M31.5, M31.6). The AAV group included three patients with polyarteritis nodosa because it was clinically the most applicable group for those patients. Depending on the classification on vasculitis, there is an overlap between AAV and PAN (Watts et al., 2007) and the affected vessel-sizes also overlap. Treatment procedures and need for hospitalization have several similarities. For those reasons, it was considered that the AAV group was clinically most relevant for those few PAN patients.

4.5 Statistical analysis

Normally distributed continuous variables were expressed as mean (+/-SD). Skewed continuous variables were reported as median [IQR]. Categorical variables were described with absolute and relative (percentage) frequencies. An independent sample t-test or Mann-Whitney U test were used to compare continuous variables as appropriate. Chi-Square or Fischer's exact test were applied to determine the significance for categorical variables. In study III, a one-way Anova or Kruskall-Wallis test was used to compare multiple groups, and significance values were adjusted by the Bonferroni correction for the multiple tests. In study III, the linear models were used to study the impact of different factors on the total costs. Due to skewed distribution, some factors were log-transformed for the linear models. IBM SPSS Statistics software versions 24 and 26 were used to perform all analyses.

4.6 Ethical considerations

All studies were approved by the Institutional Review Board of Turku University Hospital. In study I, the institutional ethics committee approved the study protocol, as appropriate. In studies I and II, patients gave a written informed consent. In study III, informed consent was not required due to the nature of the study. All studies adhered to the Declaration of Helsinki.

5 Results

5.1 Patients with a suspicion of systemic vasculitis: Impact of ^{18}F-FDG-PET/CT on the diagnostic process (Study I)

5.1.1 Patient characteristics, laboratory findings and final diagnosis

All patients were prospectively referred to this study by the treating physician. The indication for ^{18}F-FDG-PET/CT imaging was a suspicion of systemic vasculitis. Of 82 patients, 38 (46%) were male (*Table 6*). The mean age of patients was 63 years (range= 19–89 years). Common clinical symptoms were fever >38 °C (48/79 patients, 61%), hematuria (38/75, 46%) and myalgia (36/79%, 44%). New headache was significantly more common in vasculitis patients than in non-vasculitis patients, 29% vs 7% (p=0.008).

Of 82 patients, 38 (46%) had a final diagnosis of vasculitis. The most common single vasculitis diagnosis was LVV (n=14, 37%). Among patients who did not have vasculitis, the most common diagnostic entities were autoimmune disease other than vasculitis (n= 18, 41%) and infection (n=12, 27%) *(Figure 2)*.

CRP was abnormally high in 75 patients (92%) with a mean value of 129 mg/L (SD=90 mg/L). Among 38 vasculitis patients, significantly higher CRP values were detected in patients with a positive ^{18}F-FDG-PET/CT scan compared with those with a negative ^{18}F-FDG-PET/CT scan (mean CRP= 155 mg/L; SD 100 mg/L vs 90 mg/L; SD 56 ml/L, respectively; p=0.018). There was no difference in procalcitonin values between the groups (data acquired from 62 patients).

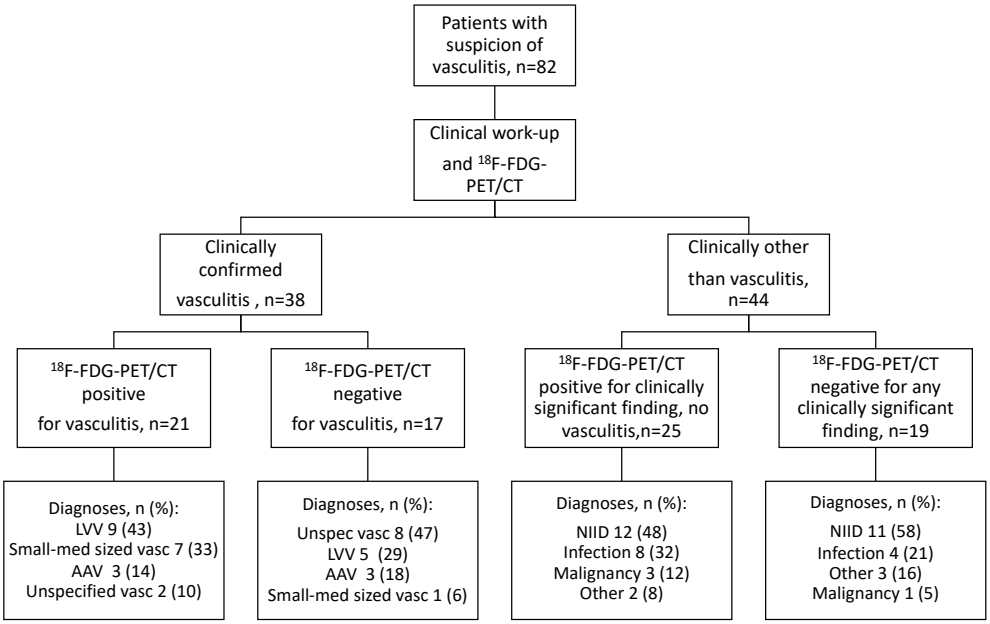

Figure 2. Study I: 82 patients with a clinical suspicion of vasculitis referred for ^{18}F-FDG-PET/CT were included. Diagnoses were confirmed by consensus-based decisions made by specialists after evaluation of a standard extensive work-up, ^{18}F-FDG-PET/CT scan and a minimum of 6 months follow-up. Vasculitis patients with a negative ^{18}F-FDG-PET/CT for vasculitis had other minor findings in PET/CT: mild infection (n=2, 12%), pericarditis (n=1, 6%) and pleuritis (n=1, 6%). Among non-vasculitis patients, clinically significant ^{18}F-FDG-PET/CT findings were: NIID (n=12), infection (n=8), malignancy (n=3) and miscellaneous (n=2). LVV=large-vessel vasculitis. AAV=antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, NIID=non-infectious inflammatory disease other than vasculitis (reproduced under terms of the Creative Commons Attribution Licence from (Taimen et al., 2019).

5.1.2 ^{18}F-FDG-PET/CT imaging findings

A clinically significant or abnormal ^{18}F-FDG-PET/CT imaging finding was detected in over half of the patients (46/82 patients, 56%) (*Table 5*). 21 patients had increased ^{18}F-FDG uptake in their vessels walls compatible with vasculitis. There was no unusual ^{18}F-FDG accumulation in the vessel walls of the 44 patients, who were not diagnosed with vasculitis. PMR is an important differential diagnosis when suspecting systemic vasculitis. There were 5 patients with a final diagnosis of PMR. Of those, one patient had ^{18}F-FDG uptake in the shoulder area related to PMR and one patient had panniculitis; the others had no clinically meaningful ^{18}F-FDG-PET/CT findings.

There were 21 patients who underwent an ^{18}F-FDG-PET/CECT and of these 6 (29%) patients had positive PET scans for vasculitis (2 GPA, 2 GCA, 2 nonspecified vasculitis). CECT was evaluated separately, and it did not reveal characteristic

vasculitic findings such as uneven enhancement, aneurysms or marked wall thickening without signs of atherosclerosis. However, atherosclerotic changes such as calcified walls with no or mild uniform enhancement in the vessel walls were common (11/21, 52%).

Table 5. Final clinical diagnosis and significance of PET/CT by diagnosis, modified from (Taimen et al., 2019) (Study I). Only diagnoses with three or more cases are presented.

CATEGORY	NUMBER OF CASES	CLINICALLY SIGNIFICANT PET FINDING
Other autoimmune diseases	18	10/18
Adult-onset Still's disease	3	0/3
Large vessel vasculitis	14	9/14
Giant cell arteritis	13	9/13
Infection	12	8/12
Infection NAS/FUO	3	2/3
Deep abscess	3	2/3
Nonspecified vasculitis*	10	2/10
Vasculitis NAS	8	2/8
Small-and medium-sized vessel vasculitis (other than AAV)	8	7/8
AAV	6	3/6
EGPA	3	1/3
Polymyalgia rheumatica	5	2/5
Malignancy	4	¾
Lymphoma	3	2/3
Miscellaneous	4	¼

AAV=ANCA (antineutrophil cytoplasmic antibody) associated vasculitis, EGPA=eosinophilic granulomatosis with polyangiitis, FUO= fever of unknown origin, NAS= non aliter specificatus *Vasculitis diagnosis confirmed by either imaging or biopsy.

5.1.3 Effect of glucocorticoid treatment on ^{18}F-FDG-PET/CT findings among the vasculitis patients

The use of glucocorticoid had a significant effect on the results of ^{18}F-FDG-PET/CT scans. In our study, 38 patients had a vasculitis diagnosis and of those patients, 9 (24%) had no previous GC treatment and 8 (21%) had used GC more than one month. Vasculitis patients with positive ^{18}F-FDG-PET/CT had significantly fewer days of

GC use prior to imaging than patients with negative ^{18}F-FDG-PET/CT (median=4 [IQR 9] vs 7 [IQR 154] days, p=0.034) (*Table 6)*. Of patients who were scanned within three days of GC therapy, 77% had increased ^{18}F-FDG accumulation consistent with vasculitis in comparison to 42% among patients imaged after one week of treatment. Among the 38 patients with vasculitis, there was a significant association of ^{18}F-FDG-PET/CT positivity with a lower GC dose on the scanning day with a median dose 15 [IQR 40] mg/day vs 40 [IQR 30] mg/day (p=0.004) (*Table 6).*

The use of GC was more frequent among patients who were later diagnosed with confirmed vasculitis. Vasculitis patients had a significantly higher prednisolone dose during ^{18}F-FDG-PET/CT scan than patients without vasculitis, median 30 [IQR 33] mg/day vs 1[IQR 20] mg/day, respectively (p=0.001). Among vasculitis patients, nine (24%) had no GC on the ^{18}F-FDG-PET/CT scanning day in comparison to the non-vasculitic group, where 24 patients (55%) used no GC on scanning day.

Table 6. Patient demographics and glucocorticoid use (Study I)

	VASCULITIS (N=38)		**NO VASCULITIS (N=44)**	**P-VALUE**
Female sex, n (%)	23 (60.5)		21 (47.7)	0.246
Age, years, mean (SD)	66.3 (13.4)		59.5 (17.5)	0.056
CRP max, mg/l, mean (SD)	125.8 (88.3)		131.8 (91.4)	0.765
Prednisolone at the time of scanning, mg, median [IQR]	30.0 [33]		1.0 [20]	0.001*
- patients using prednisolone (n)	29/38		20/44	
Prednisolone prior scanning, d, median [IQR]	6.0 [11]		0.0 [52]	0.135
	18F-FDG-PET/CT positive (n=21)	18F-FDG-PET/CT negative (n=17)		
Prednisolone at the scanning moment, mg, median [IQR]	15.0 [40.0]	40.0 [30.0]		0.004*
Prednisolone prior to scanning, d, median [IQR]	4.0 [9]	7.0[154]		0.034*

SD=standard deviation, CRP=C-reactive protein, IQR=interquartile range, *significant P-value < 0.05

5.2 G-CSF and chemotherapy induced LVV: patient case series and systematic literature review (Study II)

5.2.1 Case series of six patients

Our case series consisted of six female patients who had breast cancer and were treated in Turku or Helsinki University Hospitals between 2016 and 2018. They all received chemotherapy, including docetaxel. All patients received G-CSF which was usually administered one day after chemotherapy.

Patients developed symptoms compatible with LVV within eight days after the last G-CSF dose and nine days after the last dose of chemotherapy, which was docetaxel in 5/6 and FEC (fluorouracil, epirubicin, cyclophosphamide) in 1/6. Common symptoms were fever, chest/neck pain and general malaise. The onset of the disease and the clinical symptoms were remarkably similar between patients.

Imaging showed pathological findings in vessel walls and in perivascular tissue. CT visualized diffuse thickening of vessel walls and a perivascular mass (*Figure 3*). Upon MR imaging, there was increased signal intensity indicating edema around the vessels on T2-weighted fat saturation/STIR images and perivascular contrast enhancement in the same areas on T1-weighted images. Ultrasound visualized diffuse and hypoechoic wall thickening in affected vessels (*Figure 3*).

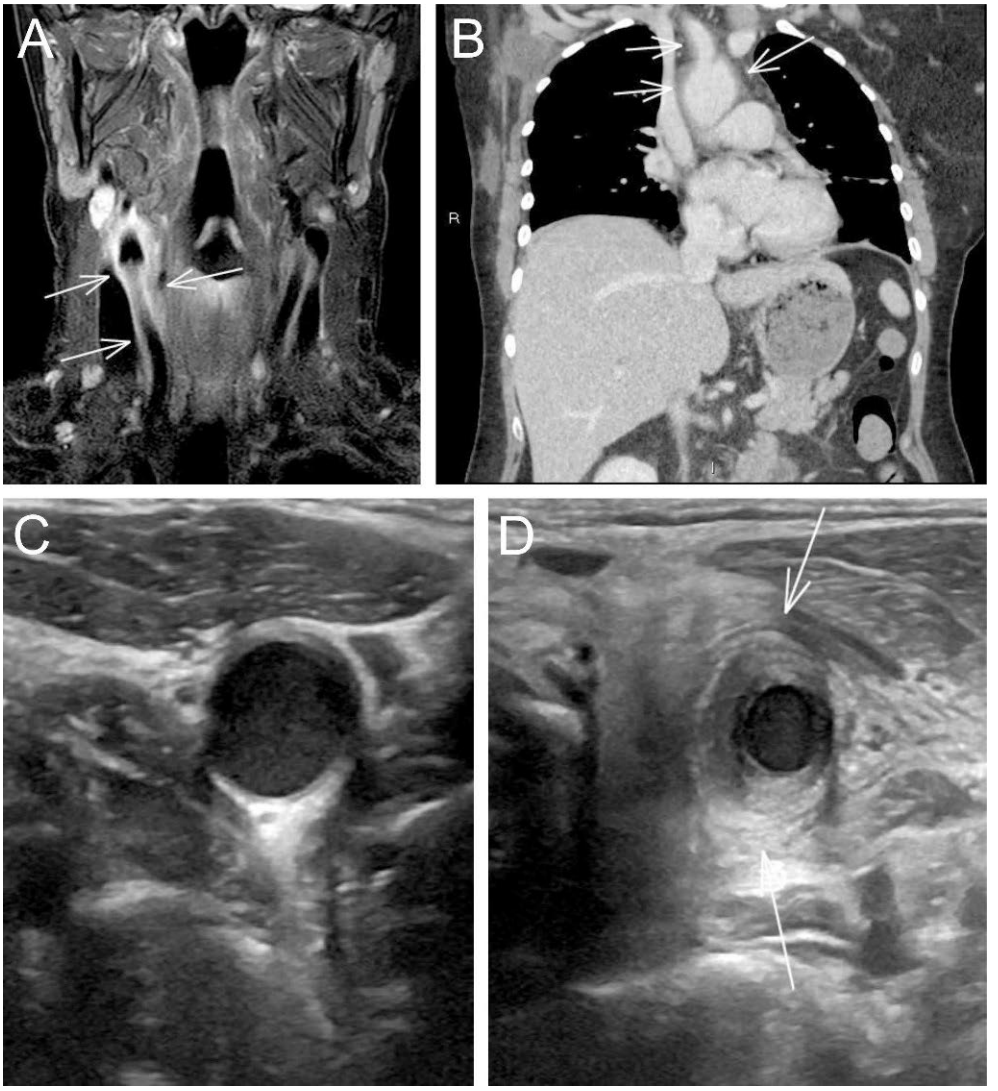

Figure 3. Different imaging techniques showing inflammation of the carotid artery and aorta. A. MR imaging showing perivascular increased signal intensity around the right common carotid artery (CCA). B. CT shows diffuse wall thickening in the thoracic aorta and in the arteries ascending from the aortic arch C. US imaging of both CCA showing normal right CCA and D. pathologic left CCA with a hypoechoic and thickened wall.

5.2.2 Literature review search results

Two separate systematic literature searches were performed to fully cover the connection between chemotherapy, G-CSF and LVV. This strategy resulted in a total of 1624 records from MEDLINE. Fifty-one case reports (48 articles) were assessed in detail after which 27 cases were excluded: 14 patients did not receive

chemotherapy nor G-CSF, 6 patients used cancer immunotherapy treatments which have a known connection with immunological adverse effects, 4 cases had no LVV, 5 cases did not provide sufficient information on chemotherapy for data analyses, 1 case had mechanical injury of the aorta, 1 case had an 18-year delay between drug administration and symptoms, 1 case had LVV prior to the treatment and 1 case had too limited data to assess ADR. 18 patients met our criteria and were included in the study.

When literature search results and our case series were merged, 24 cases were included in the study.

5.2.3 Clinical characteristics, cancer types and vasculitis distribution of all patients (n=24)

Most patients were female 18/24 (75%), and the mean age was 59 years (range=40–77 years). The most common cancer types were breast cancer 10/24 (42%) and hematological malignancies 7/24 (29%). The most common symptoms related to LVV were fever 21/24 (88%), neck pain 12/24 (50%) and chest pain 10/24 (42%). Imaging showed inflammation in the thoracic aorta and supra-aortic vessels in 17/24 (71%) patients. 5/24 (21%) patients were reported to have inflammation only in the carotid artery area. For detailed information of all 24 patients, see supplementary table in Taimen et al., 2020.

5.2.4 Drug history in relation to vasculitic manifestation in all patients (n=24)

LVV symptoms started on average 5 days (range =1–8 days) after the last G-CSF and on average 9 days (range =1–21 days) after the last administration of chemotherapy. Different types of G-CSF were used (data available in 16/24 cases): filgrastim (5 cases), pegfilgrastim (4 cases), lipefilgrastim (3 cases), unspecified product (2 cases), lenograstim (1 case) and combination of filgrastim and pegfilgrastim (1 case). Within the past year, chemotherapy was given to most patients (23/24, 96%). Many patients received combination chemotherapy with different agents, but docetaxel was the most common single medication and was received by 11/23 (48%) patients. It was also mostly used as monotherapy (4 patients). Other anticancer monotherapies were decitabine and gemcitabine, in one patient each. For statistical analysis, only exact temporal data was used and less detailed data (e.g., during the 1st cycle of chemotherapy) was abandoned. The temporal data of drug administration was available for 13/16 of G-CSF cases and for 16/23 of chemotherapy cases (including all breast cancer patients).

The authors of the case reports had different views on the etiologies of LVV. Based on the reports, G-CSF and chemotherapy were given in combination to 15 patients: 9 literature cases and our six cases. When looking at those nine previously published cases, in seven articles the authors presumed G-CSF to be the main cause of LVV even though patients received concomitant chemotherapy (Adiga et al., 2009; Chino et al., 2018; Fukui et al., 2018; Ito et al., 2017; Parodis et al., 2019; Sato et al., 2017). In one report, LVV was assumed to be caused by either chemotherapy or G-CSF (Hayashi et al., 2014). One case report considered chemotherapy alone to cause LVV although the patient also received G-CSF (Eyre et al., 2014). In eight cases from the literature, there was no data indicating whether G-CSF was used or not. Out of those eight reports, in four cases chemotherapy was considered to cause LVV as an adverse drug reaction (Azar & Fischer, 2012; Bendix et al., 2005; Chan et al., 2015; Ramsay et al., 2010). In the remaining four cases, patients were suffering from hematological malignancies and the possibility of a drug reaction was not discussed. Instead, in two cases LVV was considered as a paraneoplastic phenomenon (Fleming et al., 2012; Hausmann et al., 2016).

5.3 Delay and costs of diagnosing systemic vasculitis in a tertiary-level clinic (Study III)

5.3.1 Patient characteristic and diagnoses

By searching the hospital database from 2010 to November 2018, 450 eligible patients with a new vasculitis diagnosis were identified. Of those, 317 fulfilled the study criteria and were included in the study. The mean age was 67.1 years (range =16.9–94.7 years), and 184 (58%) of the patients were female. The most common vasculitis diagnoses were: GCA (n=132, 42%, ICD-10 code M31.5); IgAV (n=43, 14%, ICD-10 code D69.0) and GPA (n=41, 13%, ICD-10 code M31.3). The patients were grouped as described in Materials and Methods. The demographics are presented in *Table 7*.

Table 7. Demographics of the patients (Study III).

Disease group	LVV (n=141)	AAV (n=112)	IgAV (n=64)	p-value[1]
Age in years, mean (SD)	73.1 (9.5)	65.6 (13.9)	56.3 (22.1)	p<0.001[a,b,c]
Sex, female, n (%)	99 (70.2)	57 (50.9)	28 (43.8)	p<0.001[a,b]
Maximum CRP[2], mg/l, mean (SD)	92.3 (81.5)	107.3 (97.5)	62.6 (65.4)	p<0.01[b,c]
Diagnostic delay[3], days, median (IQR)	5.0 (13)	22.5 (38)	9.5 (25)	p<0.001[a,b,c]
Hospitalization time within the diagnostic period, days, median (IQR)	5.0 (5)	10 (12)	7.0 (12)	p<0.001[a,c]
Hospitalization time within 12 months[4], days, median (IQR)	7.0 (11)	22.0 (22)	13.5 (22)	p<0.001[a,b]
PET/CT performed within 12 months[4], n	25	19	3	

[1] p-value across all groups. Significant values expressed between the groups: a. LVV vs. AAV, b. LVV vs. IgAV, c. AAV vs. IgAV. [2] Highest CRP value available closest to the diagnosis.
[3] Diagnostic delay: timeline between the first contact to the tertiary health care and the date of vasculitis diagnosis. [4] 12 months forward starting from the first contact to the tertiary health care.
LVV, large-vessel vasculitis; AAV, antineutrophil cytoplasmic antibody-associated vasculitis; IgAV, IgA vasculitis and other small-vessel vasculitis; SD, standard deviation; CRP, C-reactive protein; IQR, interquartile range; PET/CT, positron-emission tomography/computed tomography.

5.3.2 Diagnostic delays in tertiary health care

The diagnostic delay in the tertiary health care center (meaning the delay from the first referral to the tertiary-level clinic to diagnosis) was longest among the AAV patients (median =22.5 [IQR 38]) days and shortest in the LVV group (median =5 [IQR 13]) days and *(Table 7).* There were 21 patients who had no diagnostic delay. Most of those patients (n=15) had LVV (11% of all LVV patients) and 5 had IgAV patients. In the LVV group, the diagnostic delay was significantly longer in males (n=42) than in females (n=99) with a median of 10 (IQR 24) days and 5 (IQR 9) days, respectively (p=0.034). In the other patient groups, sex was not a significant factor for delay. Age did not correlate significantly with the diagnostic delay in any group.

5.3.3 Costs and factors associated with high costs in tertiary health care

The total costs during the diagnostic period were the lowest in the LVV group with a median of €3123 (range =€0–28691) and the highest in the AAV group with a median of €6754 (range = €550–106.416). When examining the one-year period, defined as one year after the first contact to the tertiary health care, similar trends were seen as the highest cost was in the AAV group (*Table 8*).

There was a statistically significant positive correlation between the diagnostic delay and the total costs both during the diagnostic period and during the one year-

period (r_s=0.38, p<0.001 and r_s=0.34, p<0.001, respectively). The number of laboratory studies and hospitalization days were the strongest predictors (p<0.001) of higher costs during the diagnostic period by using the linear model. The diagnostic delay correlated statistically significantly with the total costs in this model (p<0.05) while sex, diagnosis, age, a PET/CT scan, or the CRP value did not. Coefficient of determination, R^2, for this model was 0.705. Similar results were seen within the one-year period, as inpatient days and the number of laboratory tests were the strongest predictors (p<0.001), but the diagnostic delay was no longer a significant factor in this model. Seven AAV patients underwent dialysis, but due to a low number of patients, dialysis was not included in the linear model. Dialysis was a significant cost contributor since dialysis patients' median costs were €24,651 (IQR €18 300) for the diagnostic period and €55,164 (IQR €61629) over 12 months. The costs were 3.6 and 3.4 times higher, respectively, than the median cost of the AAV patients (p<0.005 and p<0.001, respectively).

A PET/CT scan had no significant effect on the costs within the diagnostic period or within one-year period when using a linear model including effects of sex, diagnostic delay, CRP value, the number of laboratory studies, the number of inpatient days and diagnosis. Forty-seven patients underwent a PET/CT scan and vasculitic findings were seen in 27 patients (60%), most of those being LVV (16 cases). Patients with a diagnostic PET/CT had mean 16.5 days (range = 0–31 days) of hospitalization within the diagnostic period. In comparison, the mean diagnostic hospitalization period was 9.4 days in the whole study population.

Table 8. Costs of diagnostic studies within the diagnostic period[1] and over the first 12 months[2] (Study III).

Disease group	LVV (n=141)	AAV (n=112)	IgAV (n=64)	p-value[3]
Diagnostic period, days, median (IQR)	5.0 (13)	22.5 (38)	9.5 (25)	p<0.001[a,b,c]
Laboratory costs, €, median (IQR)	242.5 (432.9)	1024.9 (1049.6)	547.0 (755.3)	p<0.001[a,b,c]
Radiology costs, €, median (IQR)	189.0 (451)	357.0 (657)	76.0 (185)	p<0.001[a,c]
Total costs, €, median (IQR)	3123.0 (4517.3)	6754.5 (8812.9)	3346.1 (6371.5)	p<0.001[a,c]
12-month period				
Total costs, €, median (IQR)	6605.2 (7681.1)	16169.5 (19193.6)	10049.4 (15137.8)	p<0.001[a,b,c]

[1] Diagnostic period: timeline between the first contact with the tertiary health care and the date of vasculitis diagnosis. [2] 12 months after the first contact with the tertiary health care. [3] p- value across all groups. Significant values expressed between the groups: a. LVV vs. AAV, b. LVV vs. IgAV, c. AAV vs. IgAV. LVV, large-vessel vasculitis; AAV, antineutrophil cytoplasmic antibody-associated vasculitis; IgAV, IgA vasculitis and other small-vessel vasculitis than AAV; IQR, interquartile range.

6 Discussion

This study focused on clinical challenges in diagnosing vasculitis and elucidated the sometimes the difficult and laborious diagnostic process for accurate vasculitis diagnosis. Both for the patient and for society, a swift and precise diagnosis is a benefit.

6.1 Clinical impact of using ^{18}F-FDG-PET/CT in the diagnosis of suspected vasculitis

During the past decade, accumulating evidence has shown that ^{18}F-FDG-PET/CT is effective in diagnosing suspected vasculitis, especially in large arteries. So far, most of the study cohorts have been small with variable study criteria, which is why additional studies have been needed to validate the efficacy.

In Study I we demonstrated that in a real-life cohort of patients with suspected vasculitis, ^{18}F-FDG-PET/CT showed vasculitis in 26% of all patients. In line with the previous studies, most of the vasculitides diagnosed with ^{18}F-FDG-PET/CT were LVV (Prieto-González et al., 2015; Schönau et al., 2018). However, a less evident finding was, that in this cohort, ^{18}F-FDG-PET/CT was able to show evident vasculitic findings also in smaller vessels and thus, confirm the vasculitis diagnosis. A previous case report showed that in case of a strong vascular inflammation in AAV, the vasculitic findings can be seen as a tree root-like uptake pattern (Salomäki et al., 2014). Similar patterns were observed in our study in seven patients who had a final diagnosis in the category of small-medium vessel vasculitis or unspecified vasculitis. Clinically, this was essential information to guide treatment.

In the same cohort, 21 patients received contrast enhancement for the CT study (CECT). In the literature, there is little data about the usefulness of ^{18}F-FDG-PET/CECT compared with ^{18}F-FDG-PET/CT in diagnosing vasculitis. Muto et al. examined 88 elderly patients with ^{18}F-FDG-PET/CT and CECT. Thirteen had aortic thickening in CECT, and all had distinct FDG accumulation at the corresponding sites. ^{18}F-FDG-PET/CT also showed additional vascular inflammation sites (Muto et al., 2014). Lariviere et al. compared FDG-PET and CTA and found that both methods had a strong diagnostic yield for diagnosis of GCA, but FDG-PET had

higher positive predictive value (Lariviere et al., 2016). Our study is in line with these findings since CECT did not yield additional information about vasculitic findings when compared with ^{18}F-FDG-PET/CT. Six patients had evident vasculitis in ^{18}F-FDG-PET, but none had vasculitic findings in CECT. Atherosclerotic findings were common in CECT.

The EULAR recommendations consider PET useful due to its ability to also identify other serious conditions than vasculitis (Dejaco et al., 2018). This is supported by our results as ^{18}F-FDG-PET/CT revealed clinically significant information in more than half of the patients in our cohort. Significant PET/CT findings were common in infections, malignancies and in other autoimmune diseases such as myositis (*Table 5*). This was often essential information to guide further work-up. From the clinician's perspective, a negative ^{18}F-FDG-PET/CT finding is also reassuring. Balink et al. found that in inflammation of unknown origin (IUO), ^{18}F-FDG-PET/CT has a high negative predictive value and is helpful to identify patients who have a self-limiting or benign disorder (Balink et al., 2014).

Our study supports the idea that ^{18}F-FDG-PET/CT is useful especially in situations where a first line vascular ultrasound is not able to confirm the LVV diagnosis. The spectrum of conditions causing vasculitis-like symptoms is wide. Behind the suspicion of vasculitis may lie an infection, a malignancy or vasculitis of smaller sized vessels. In those cases, ^{18}F-FDG-PET/CT is helpful.

6.2 Effect of glucocorticoid treatment on ^{18}F-FDG-PET/CT results

The effect of the use of glucocorticoid (GC) medication on the diagnostic accuracy of ^{18}F-FDG-PET/CT is a major concern (Fuchs et al., 2012). In Study I we found that a shorter duration of GC therapy is significantly associated with positive ^{18}F-FDG-PET/CT vasculitic findings. More specifically, vasculitis patients with positive and negative ^{18}F-FDG-PET/CT imaging had a median of 4 and 7 days of prednisolone use, respectively. This agrees with the results of an important study by Nielsen et al. They showed that the diagnostic performance of ^{18}F-FDG-PET/CT in LV-GCA remains unchanged within the first three days of GC treatment but significantly decreases after 10 days of GCs (Nielsen et al., 2018). Although the ^{18}F-FDG-PET/CT was positive in every patient at day 3, there was already a 10-15% decrease in FDG uptake compared with the baseline PET. The number of patients in this study (n= 24) was low, thus further confirmation with a larger population is required. In 2014, Prieto el al. reported a prospective study evaluating FDG uptake in patients who had a new, biopsy-proven diagnosis of GCA. They did not find any difference in diagnostic sensitivity between treatment naïve patients and those treated with GC for ≤ 3 days (Prieto-González et al., 2014). Imfeld et al. showed that

prednisolone use for 10 days or more significantly reduced ^{18}F-FDG-PET/CT sensitivity and the earliest sign of lowered sensitivity was seen in the abdominal aorta after 3 days of treatment (Imfeld et al., 2017). One small study surprisingly found no connection between GC treatment and vascular FDG uptake scores, and the uptake was increased in most patients with GCA despite exposure to prednisolone. In that study, the sensitivity was lower than previously reported, probably because of the GC treatment (Clifford et al., 2017).

In our cohort, a lower GC dose at the time of imaging was also significantly associated with an ^{18}F-FDG-PET/CT-based vasculitis diagnosis. There is very limited data on this subject and further studies are needed to confirm if this is a clinically significant finding or not.

Based on the recent literature and our results, GC treatment < 3 days does not reduce the diagnostic accuracy of ^{18}F-FDG-PET/CT to detect LVV. However, in many centers it is not possible to perform ^{18}F-FDG-PET/CT within that time window. In that case, other imaging modalities must be considered but the limitations of GC treatment on those modalities must be taken into account. More data is needed to answer the question how the diagnostic sensitivity of ^{18}F-FDG-PET/CT is reduced between 3–10 days after treatment initiation.

6.3 Is ^{18}F-FDG-PET/CT worth the money in diagnosing vasculitis?

^{18}F-FDG-PET/CT is an expensive method of investigation. In Turku University Hospital, the average price for a single infection/inflammation targeted whole body ^{18}F-FDG-PET/CT scan from vertex to toes was approximately €2150 in 2020. Despite the high price, we found that ^{18}F-FDG-PET/CT was not a significant contributor to total costs in the diagnostic work-up of patients with systemic vasculitis. There is no reliable published data about the cost-effectiveness of ^{18}F-FDG-PET/CT in diagnosing vasculitis. Balink et al. published an interesting pilot study of 92 patients concerning cost-effectiveness of ^{18}F-FDG-PET/CT in IUO (Balink et al., 2015). In their retrospective study, NIID (noninfectious inflammatory disease) was the most common diagnostic group, and 19 LVV/PMR diagnoses were made with ^{18}F-FDG-PET/CT. Considering the amount of vasculitis patients, this study partly reflects the same question as our Study III. Balink et al. found that the diagnosis was reached more frequently among patients (32/46) who underwent ^{18}F-FDG-PET/CT. The mean cost per patient including hospitalization was €5,298. In IUO patients without ^{18}F-FDG-PET/CT, the diagnosis was reached in 14/46 patients and the cost per patient was significantly higher (€12,614). Balink et al. concluded that in IUO ^{18}F-FDG-PET/CT has a potential to fasten the diagnostic process, to decrease the number of unnecessary diagnostic tests and shorten hospitalization time.

This is in accordance with our results. In our study III, patients who received ^{18}F-FDG-PET/CT had longer hospitalization, causing notable costs. In theory, earlier performed ^{18}F-FDG-PET/CT could be cost saving if inpatient days were decreased. As discussed in 6.2, GC treatment for more than 3 days increases the rate of a false negative scan. Therefore, avoiding ^{18}F-FDG-PET/CT scanning in patients who receive long GC treatment, seems cost-beneficial.

In the era of an increasing number of diagnostic imaging tools, there is a need for reliable data of cost-effectiveness with different imaging modalities. Regarding ^{18}F-FDG-PET/CT and systemic vasculitis, further studies are needed to gain understanding of which patients benefit the most from early ^{18}F-FDG-PET/CT in order to get a rapid and cost-effective correct diagnosis.

6.4 Diagnostic delay in systemic vasculitis

Previous studies report great variability in the diagnostic delay in patients with systemic vasculitides (Hočevar et al., 2019; Pearce et al., 2018; Prior et al., 2017; Sreih et al., 2019; Takala et al., 2008). This was confirmed in Study III, which was based on manually validated diagnoses and key pivotal dates. This type of data is very reliable in comparison with pure registry data where the risk of incorrect diagnoses is significant.

Our study focused on the diagnostic delay in tertiary-level health care. Data from primary and secondary care were not available in our hospital database. As expected from previous studies, the diagnostic delay was shortest in the LVV group. In this group, 11% of patients got a diagnosis of GCA without any delay, most often in the emergency department. On the other hand, 26% of patients had a diagnostic delay of more than 15 days in the tertiary-level. Males experienced significantly longer delays. A large meta-analysis shows that patients with non-cranial LVV have a clearly longer delay from symptom onset to diagnosis than cranial-LVV patients (Prior et al., 2017). Non-cranial clinical presentation of LVV could be associated with a longer delay also in our study. From this same cohort of patients, we have unpublished data of 140 GCA patients showing that non-cranial GCA presentation is a significant factor for longer diagnostic delay when examining delay from early symptom onset to diagnosis.

In our study, the AAV group had the longest median diagnostic delay, and the range was very wide. 76 (68%) patients had a delay of more than 15 days and of those, 24 (21%) over two months. In AAV, Pearce et al. reported a median diagnostic delay 2.6 months (IQR 1.2-6.1) from symptom onset to diagnosis (Pearce, McGrath, et al., 2018). Among inpatients, the delay from admission to diagnosis ranged from 0 to 53 days representing a similarly wide range as in our study. The overall delay was longer in our study, but our analysis included the total delay in tertiary health

care, not only inpatient days. In another study, Pearce et al. showed that increased health-seeking behavior already starts many years prior to diagnosis suggesting that patients are being unwell for a long period without a diagnosis. Especially some clinics, such as ear-nose-throat, ophthalmology and rheumatology, show frequent attendance and are key players in early diagnosis (Pearce, Hubbard, et al., 2018).

Among patients with IgAV, the median diagnostic delay was 9.5 days, which is in line with a recent prospective study showing a median symptom duration of 7 days (Hočevar et al., 2019). This short delay probably reflects the fact that many IgAV symptoms, such as purpura and melena, are easily recognizable and skin biopsy is accessible.

Our study was able to identify the patients with long delays. However, this study was not designed to analyze the caveats in the diagnostic work-up. Future studies are needed to better recognize the characteristics of patients with long latency of diagnosis in order to reduce that delay.

6.5 Costs in diagnosing systemic vasculitis and how the diagnostic delay affects the costs

There is surprisingly little published data on the costs of diagnostics of the systemic vasculitides. Study III focused on the direct costs during the diagnostic period and within one year after the first referral. It is known that the vasculitis diagnostics is challenging, and the diagnostic work-up may lead to increased financial costs. We found that patients with AAV had the highest diagnostic costs, with a median of €6800. The LVV group of patients had the lowest costs, with a median of €3100. The one-year median total costs were €16,200 and € 6605, respectively. The range of costs in all groups was very wide. Overall, the inpatient days and number of laboratory tests were the strongest predictors of higher costs in all groups.

Previously published studies have reported the economic burden of systemic vasculitis from a different viewpoint or with a different patient selection than ours. Only one study included various systemic vasculitides and found that vasculitis patients had double the higher annual heath care expenditures compared with their counterparts without systemic vasculitis among Medicare federal insurance beneficiaries (Thorpe et al., 2018). Other studies have concerned separate disease groups. Most of the few studies cover GCA and AAV; previous data of the costs of adult IgAV do not exist. Our results are in line with previous studies showing that in general AAV patients produce higher expenses than GCA patients (Babigumira et al., 2017; Mounié et al., 2018; Quartuccio et al., 2020; Raimundo et al., 2015; Valent et al., 2019).

The Finnish health care system, as well as the systems of many other European countries, follow a tax-funded model which is completely different from the

insurance-based systems. With that premise, health care costs from the insurance-based systems, such as in the US, are not directly comparable to our results. For example, two studies on GCA, one US and one French, evaluated the incremental costs and yielded results that differed much from one another (Babigumira et al., 2017; Mounié et al., 2018).

When looking at the individual factors behind the higher costs, in many studies hospitalization is a major player (Krulichova et al., 2004; Quartuccio et al., 2020; Trieste et al., 2012; Ungprasert et al., 2020; Valent et al., 2019). This is in accordance with our results. Also, as in our study, frequent use of laboratory tests has been correlated with increasing costs (Koster et al., 2017). Another important cost factor is medication (Krulichova et al., 2004; Valent et al., 2019). We did not include costs of medication if they were given in outpatient care. The medication administrated in the hospital was included in the direct hospital billing.

In Study III we evaluated both the diagnostic delay and costs in a tertiary-level clinic and combined the data. Interestingly, we found that a longer delay had a significant positive correlation with the higher costs both during the diagnostic period and the one-year period. To our knowledge, the current study is the first to demonstrate such an association. Indirectly, a delay in achieving a diagnosis has been shown to have negative effects on the outcome in the rheumatic diseases (Aletaha & Smolen, 2018; Hocevar et al., 2016). Furthermore, disease severity has been associated with higher costs (Doria et al., 2014, 2015; Houben et al., 2017).

Overall, our results, as well as the previously referred studies, show considerable variation and a wide range in costs. They indicate that a minority of patients generate a significant proportion of the total costs. Future studies are needed to identify the characteristics of patients with high costs. Partly, some of those patients are the same as those who have a long diagnostic delay. Our study adds valuable information to the COI for hospitalized vasculitis patients and hints that a shorter diagnostic delay may lead to lower total costs.

6.6 G-CSF and chemotherapy-induced large-vessel vasculitis

In most cases, the etiology of systemic vasculitis remains unknown. Sometimes, the triggering event can be identified guiding the management of vasculitis. We identified six patients suffering from breast cancer who developed LVV during chemotherapy. This unusual phenomenon was described in the form of a patient series and evaluated together with a systemic literature review in Study II.

Our six patients had a remarkably similar clinical picture including fever, chest and neck pain, general malaise, and high levels of inflammatory markers. The symptoms started within 10 days after the last dose of G-CSF and chemotherapy.

Imaging with different modalities showed obvious inflammation of the aorta, supra-aortic vessels and/or carotid area consistent with LVV. Especially, perivascular inflammation was present. Infections were carefully excluded. The start of the symptoms in near proximity to the administration of chemotherapy and G-CSF raised a suspicion of an adverse drug reaction (ADR), which was the probable diagnosis. Discontinuation and/or change of therapy, and in some cases GC treatment, resulted in rapid improvement of vasculitic symptoms. Importantly, no relapses of vasculitis occurred in our patients after cessation of G-CSF treatment.

Our preliminary literature search was carried out in April 2018 and the final search was performed in April 2019. During this period the reported number of cases increased. We found 18 cases who met our study criteria. Four published cases were very similar to our case series, with all patients having breast cancer and a similar type of medication. Until 2018, there was a very limited number of case reports showing that LVV could be associated with G-CSF or chemotherapy. The first registry study came out in October 2018 when Lardieri et al. published a short correspondence after searching the U.S. Food and Drug Administration (FDA) adverse event reporting system (FAERS) and the medical literature. They reported 15 FAERS cases supporting the causal association between aortitis and G-CSF use (Lardieri et al., 2018). In February 2019, Oshima et al. reported the results of a Japanese adverse drug event report database identifying 25 cases of aortitis in patients with malignancies, of which, 16 cases had a possible association with G-CSF (Oshima et al., 2019). Before those reports, in February 2018, the European Medical Agency had stated shortly that “there is at least a reasonable possibility of a causal association between aortitis and G-CSF treatment” (PRAC recommendations on signals EMA/PRAC/59224/2018).

In our study, we explored the connection between LVV, G-CSF and chemotherapy even though the reports above were leaning more towards G-CSF alone. However, as chemotherapy and G-CSF are most often given in conjunction and the published literature was scarce, it was difficult to address the exact cause of ADR. The same dilemma was observed with the previous case reports as some authors have interpreted the ADR as G-CSF-associated and some chemotherapy-associated; these cases are presented in detail in a supplement table by Taimen et al. (Taimen et al., 2020). The complete medical history was unavailable for a few literature cases as the authors had reported only drugs that they considered relevant at that time. Since all our cases had malignancies, the influence of a paraneoplastic syndrome as part of the etiology of LVV cannot be completely excluded. However, based on the literature, we considered this unlikely (Manger & Schett, 2014; Pelosof & Gerber, 2010). We also found 3 cases where patients without malignancy developed LVV after administration of G-CSF (Darie et al., 2004; Miller et al., 2016; Umeda et al., 2016)

Recently Lee et al. investigated the prevalence, clinical features, and treatment of aortitis in over 2000 Korean breast cancer patients receiving G-CSF. The incidence of aortitis was 0.3%. The clinical presentation and imaging findings were similar as in our case series. Treatment with moderate doses of prednisolone (0.5 mg/kg) was sufficient for improvement without complications (Lee et al., 2020). Lee et al. studied only PEGylated filgrastim which seems to be most commonly associated with LVV; however, in our study also non-PEGylated products were represented. The number of reported cases is increasing. After our literature review, there are at least 18 new published cases in 13 articles between 2019 and 3/2021. All cases had malignancies and different types of G-CSFs were used (Corral de la Fuente et al., 2020; Harada et al., 2021; Hoshina & Takei, 2019; Kametani et al., 2021; Kawahara et al., 2020; Kinjo et al., 2019; Koyama et al., 2021; Lee et al., 2020; Miyazaki et al., 2020; Mukai et al., 2020; Nakamura et al., 2020; Shirai et al., 2020; Yamamoto et al., 2021).

Based on our study and currently available data, there is a high suspicion of a relation between G-CSF, chemotherapy and LVV. In the absence of large-scale data, this causality is not certain, and the mechanism is unknown. Therefore, more detailed follow-up studies with larger patient cohorts are warranted in the future.

6.7 Strengths and limitations

The strengths of Study I include its prospective setting and relative high number of patients enrolled in the study. The cohort represented real-life patient population with the diagnostic challenges that clinicians frequently meet. The major limitation was the heterogeneous patient population, which included several different types of vasculitides. Moreover, as there were no pre-defined inclusion criteria for vasculitis diagnosis the diagnosis was based on the expert's clinical judgement. Although all patients underwent ^{18}F-FDG-PET/CT, a diagnostic contrast-enhanced CT scan was not carried out for all of them systematically. However, this limitation in imaging protocol appeared not to interfere with the data analysis and the overall results.

In Studies II and III the main limitation was the retrospective nature of the studies, which is why the characterization of the patients and data collected could not be as comprehensive as in a prospective trial. Especially in Study II some published case reports lacked detailed description of the complete medical history and the extent of the imaged vascular territories. In Study III, only direct health care costs were evaluated even though patients are likely to be burdened of high out-of-pocket costs. The strength was that in both studies the pivotal dates were manually extracted and verified from the electrical patient records. In all studies the diagnoses were carefully validated by experts, which is a benefit compared with registry data

studies. In Study II, the systematic literature review emphasized the importance of reported new patient series.

6.8 Future prospects

In the future, it is important to compare the diagnostic accuracy and value of different imaging techniques with each other in prospectively collected datasets. More data is needed on how GC effects the diagnostic accuracy of different modalities, especially between 3 and 10 days of treatment. This would give more flexibility for image scheduling. This study concentrated on diagnostic challenges, but the role of imaging in monitoring LVV needs equal attention. Improved understanding of the strengths and the weaknesses of each imaging technique in vasculitis diagnosis is important in order to choose the most suitable imaging modality. This helps to minimize unnecessary tests and eventually reduce the overall costs. Regarding PET imaging, the development of novel, inflammation specific tracers, might assist in even more accurate diagnostics and monitoring of disease activity.

The diagnostic delay shows great variation. Gaining better understanding of the factors associated with long delays is needed to shorten the time to diagnosis.

In future studies it is important to explore in larger patient cohorts the relation between G-CSF, chemotherapy and LVV and to examine the incidence of drug-induced LVV in cancer patients. To our knowledge, there are multiple similar, unregistered cases in Finland. According to previous studies, many of the reported cases come from East Asia and Scandinavia, both areas where LVV has a high prevalence. Therefore, it would be tempting to explore the genetic predisposition and mechanisms behind this drug-induced LVV.

7 Summary/Conclusions

In a real-life cohort of patients with suspicion of vasculitis, ^{18}F-FDG-PET/CT was effective in revealing different types of vasculitis in over 25% of patients. Among vasculitis patients a positive ^{18}F-FDG-PET/CT was associated with fewer days and a lower dose of glucocorticoid treatment. Besides vasculitis, ^{18}F-FDG-PET/CT yielded clinically meaningful information in more than half of the patients guiding the diagnostic work-up.

The diagnostic delay is substantial, with great variability, when making the diagnosis of systemic vasculitis in tertiary-health care. This delay has a significant positive correlation with higher costs. The costs are unevenly distributed indicating that a minority of the patients generates a significant proportion of the total costs. PET/CT, although relatively expensive compared with other imaging techniques, had no significant effect on the total costs. Reducing the diagnostic delay could lower the costs.

There is a reasonable possibility of a causal association between LVV, G-CSF and chemotherapy. Diagnostic imaging is the key factor in making an LVV diagnosis. Early identification of this drug-induced LVV and quick discontinuation of the offending drug is essential for successful recovery.

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