

Diploma Thesis

**Giant Cell Arteritis (Morbus Horton)- Does this disease
influence the survival of patients?**

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Abbreviations:

ANCA	Anti-neutrophil Cystoplasmic Antibody
CCL	<i>Chemokine C-C Motif Ligand</i>
CCR	Chemokine Receptor
CD	Cluster of Differentiation
CDS	Colour Doppler Sonography
CRP	C-Reactive Protein
CT	Computerised Tomography
DC	Dendritic cell
ESR	Erythrocyte Sedimentation Rate
FUO	Fever of Unknown Origin
GC	Glucocorticoids
GP	General Practitioner
ICAM-1	Intercellular adhesion molecule
IL-1Ra	Interleukin receptor antagonist
MR	Magnetic Resonance
PAOD	Peripheral Artery Occlusive Disease
PET	Positron Emission Tomography
RANTES	Regulated on activation normal T-cell expressed and secreted
TA	Temporal artery
Th	T helper cell
TNF	Tumour Necrosis Factor

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Abstract (deutsch):

Einführung:

Riesenzellarteritis (RZA) ist eine chronische Autoimmunerkrankung älterer Patienten, welche große und mittlere Arterien betrifft. RZA beinhaltet eine lokale Entzündung in den betroffenen Gefäßen, sowie eine systemisch entzündliche Komponente. Überwiegend betroffen sind Patienten von europäischer Abstammung, mit einem Alter von über 50 Jahren. Aktuelle Forschungen fanden unterschiedliche Ergebnisse bezüglich des Einflusses dieser Erkrankung auf das Überleben von Patienten. In der Literatur finden sich Hinweise auf einen Zusammenhang zwischen RZA und erhöhten Raten an Aortenaneurysmen und Aortendissektionen.

Die aktuelle Studie ist eine retrospektive Analyse einer RZA Patientenkohorte, mit dem Ziel die Mortalität in der Patientengruppe und Zusammenhänge zwischen Mortalität und Aortenaneurysmen zu erfassen.

Methoden:

Daten von 177 RZA Patienten an der Abteilung für Angiologie des LKH Graz zwischen 1995 und 2012 wurden analysiert. 158 Patienten wurden in die Studie eingeschlossen. Daten bezüglich Diagnose, Risikofaktoren, Komplikationen, Therapien und Überleben der Patienten wurden gesammelt. Die Datensammlung erfolgte durch Analyse von Papierakten und elektronischer Akten. Fehlende Information wurde über telefonischen Kontakt mit Patienten und deren behandelnden Hausärzten vervollständigt. Für die statistische Signifikanz wurden p-Werte <0.05 angenommen.

Ergebnisse:

Die Patientengruppe setzte sich aus 112 (70.9%) Frauen und 46 (29.1%) zusammen. Das durchschnittliche Alter bei Diagnose betrug 71.4 (SD ± 9.5) Jahre. 62.7% hatten die Diagnose RZA und 37.3% hatten RZA und zusätzlich PMR. Von 158 Patienten starben während der Studie 38 (24.1%). Die rohe Sterblichkeitsrate betrug 1.41% pro Jahr in der Patientengruppe. Das durchschnittliche Alter zum

Todeszeitpunkt war 80.53 (SD±6.7) Jahre. Es wurden höhere Todesraten in der RZA Gruppe im Vergleich mit der RZA + PMR Gruppe festgestellt ($p=0.046$). Höheres Alter resultierte mit einer höheren Sterblichkeit ($p=0,023$). Ein vorangegangener Insult, Augenbeteiligung und Opticus Neuropathie standen ebenfalls im Zusammenhang mit erhöhter Sterblichkeit ($p=0.001$, $p<0.001$, $p<0.001$). Therapie mit Statinen wirkte sich positiv auf die Mortalität aus ($p=0.017$). Eine positive Biopsie wurde mit einem schlechteren Outcome in Verbindung gebracht ($p=0.001$) In dieser Kohorte fanden sich keine durch Aortenaneurysmen bedingte Todesfälle.

Fazit:

Diese Studie fand einige Faktoren, welche die Mortalität beeinflussen; höheres Alter bei Diagnose, RZA ohne zusätzliche PMR, Vorhandensein von Augenbeteiligung, ischämische Opticus Neuropathie, vorangegangener Insult, keine Statin Therapie und positive Biopsie Ergebnisse. Diese Ergebnisse sind mit der herangezogenen Literatur vergleichbar und beinhalten nützliche Informationen für den Arzt. Spezielle Patienten Subgruppen benötigen engere Überwachung, da sie ein höheres Risiko für Komplikationen haben. Es konnten keine Aussagen über Aneurysmen und Mortalität gemacht werden, da sich in dieser Patientengruppe zu wenige Fälle fanden.

Abstract (English):

Introduction:

Giant cell arteritis (GCA) is a chronic autoimmune disease of elderly patients affecting the large and medium arteries. GCA is characterized by local inflammation of the artery and systemic inflammatory response. It primarily affects people of European descent, over 50 years of age, peaking in the eightieth decade of life. Current research is not in agreement on whether GCA affects the mortality outcomes for patients, with some studies finding a higher mortality rate and some no change. There is some indication that GCA does increase aortic aneurysm and dissection related mortality.

The current study is a retrospective analysis of a cohort of CGA patients, aiming to assess the mortality outcomes for this group and any connection between aortic aneurysms and mortality.

Materials & Methods:

Records for 177 patients diagnosed with GCA at the division of Angiology at the Medical University of Graz between 1995 and 2012 were collected. The final patient group was 158 after exclusions. Data was collected for diagnostic factors, risk factors, adverse events, adjuvant therapies and survival. Data collection was through analysis of hard copy and electronic patients records. Missing information was followed up through telephone contact with the patients or their GP. Statistical significance was assumed for p-values <0.05.

Results:

The study population consisted of 112(70.9%) females and 46(29.1%) males. Average age of diagnosis was 71.4 (SD \pm 9.5) years. 62.7% patients were diagnosed with GCA alone and 37.3% had GCA + PMR. Of the 158 patients, 38 patients died (24.1%). The crude mortality rate in the patient group is 1.41% per year. The mean age at death was 80.53 (SD \pm 6.7). There was a higher occurrence of death in the patients with GCA versus those with PMR (p=0.046). Patients with an older age at diagnosis appeared to have worse mortality outcomes (p=0.023). Patients who had a history of stroke, those with ocular

manifestations and ischaemic optic neuropathy were associated with mortality ($p=0.001$, $p<0.001$, $p<0.001$). Patients taking statins had better survival than those who were not ($p=0.017$). Positive biopsy was associated with poorer outcome than a negative one ($p=0.001$). There were no reported incidences of aortic aneurysm as cause of death.

Conclusion:

This study revealed several factors to be associated with mortality in GCA patients; older age at diagnosis, GCA only disease type subgroup, presence of ocular manifestations, ischaemic optic neuropathy, history of stroke, lack of use of statins and a positive biopsy result. These results are comparable to the literature analysed and represent useful information to inform the clinician on particular patient types that need closer medical monitoring and are at higher risk for complications. No conclusions could be made on aneurysms and mortality due to lack of incidence in our study group.

Introduction:

Giant Cell Arteritis (GCA) is a systemic autoimmune disease affecting large and medium arteries especially the proximal Aorta and its branches(1). The condition can be summed up into two components; local inflammation of the artery and systemic inflammatory syndrome. The most common symptoms caused by this disease are headache, facial ache, jaw claudication and visual impairment. In addition patients with GCA often experience general fatigue, weight loss, fever and nocturnal sweating. There is no characteristic laboratory test for identification, despite patients demonstrating a wide variety of inflammatory markers. The current definite diagnosis is microscopic analysis of tissue samples from the temporal artery. The pathognomonic histological picture shows granulomas consisting of T-Lymphocytes, macrophages and giant cells typically located in the internal media junction. GCA is a disease which occurs in patients primarily over 50 years of age and has prevalence to be 1:750-1:740(2).

GCA is the highest contributor to inflammation affecting the aorta representing 75% of these patients. The chronic inflammation can cause aneurysms especially in the thoracic part of the aorta. A study in 1990 found that patients with GCA have an increase of 17 times chance of developing aortal aneurysms. This theory was tested by several other studies which also came to similar conclusions. In addition patients also were observed to have an increased cardiovascular risk.

Up to this date it is unclear whether the occurrence of aortal aneurysms in this disease leads to increased mortality.

This aim of this study was to retrospectively analyse the mortality of a large group of GCA patients treated in the department of Angiology in Graz, Austria. An additional goal was to investigate a possible connection between aortic aneurysms and mortality.

The outcome of this study could influence the current treatment plan concerning the screening for aortic aneurysm. It is questionable how much a patient will benefit from a potentially very burdening diagnosis.

GCA and Polymyalgia Rheumatica

Giant cell vasculitis was first identified in 1889, when a British surgeon noted a patient with painful red streaks on his head; he named it arteritis of the aged. In 1888 a Scottish physician treated 5 elderly patients with generalised muscle pain, which in the 1950s came to be known as the autoimmune disease Polymyalgia Rheumatica (PMR) (3). PMR is characterised by pain and stiffness in the neck, shoulder and pelvic girdle.

The relationship between the two diseases started to become apparent in the 1960's as it was increasingly recognised that PMR often occurred before, simultaneously or after onset of GCA(4) . PMR and GCA are beginning to be described as different clinic expressions of the same disease (5).

Many studies in the field of GCA concurrently evaluate symptoms of PMR in their cohorts. There are conflicting results on whether PMR and GCA share a common genetic background (4). Key connections between the two diseases are the older age at onset, increasing incidence > 50 years of age, higher occurrence in women than men, increase of acute phase reactants before treatment, and rapid response to glucocorticosteroids (6). Sixteen to twenty-one percent of patients with PMR also have GCA, and forty-sixty percent of patients with GCA also have PMR (6). The prognosis for PMR is more favourable than GCA with less adverse events reported (4).

Epidemiology:

The actual prevalence of giant cell arteritis remains unknown. A Swedish post-mortem study estimated prevalence to be 1:750-1:740 in persons older than 50 years. (2)

Most epidemiological studies on GCA have been carried out in Caucasian populations. Diagnosis criteria for these studies differ, some using temporal artery biopsy only (live or post mortem), or in combination with clinical findings (7-9). Different methods and diagnostic criteria make it difficult to compare studies; particularly, some consider only CGA whilst others group PMR with GCA.

Overall there appears to be general increase in incidence in different parts of the world such as Minnesota, Israel, Spain, UK and Goteborg Sweden(2,10-12).**Fehler! Verweisquelle konnte nicht gefunden werden.Fehler! Verweisquelle konnte nicht gefunden werden.** summarises some of the epidemiological studies and their results- note the significant differences in males and females, and primarily Caucasian populations versus other ethnicities.

Incidence by ethnicity:

GCA appears to be most frequent in people of Caucasian descent. The highest incidence of GCA has been reported in northern European/ Scandinavian countries of Denmark (13), Iceland, (14) and Sweden (15) with incidences up to 76.6/100,000 in people over 50 years (13).

Much lower rates occurred in the Mediterranean (6.9/100,000 >50)(16), Middle Eastern (12,17), and Asian (1.47/100,000 >50)(18) populations.

GCA was found to be less frequent in Tennessee than in other similar studies, it has to be noted that 42% of the study population were African American and the incidence was seven times higher in the white population compared to the African American patients (9).

A 2006 study in the UK supports the trend of a north-south decrease of the incidence in Europe, moving away from Scandinavia to lower Europe, with incidence rates sitting between these areas (11).

The Olmsted County study in Minnesota showed the next highest incidence outside of northern Europe (17/100,000 >50)(7).

Studies in non-Scandinavian countries that had higher incidence rates than had

populations of primarily European and particularly Scandinavian ancestry (7). It has been suggested that Scandinavian countries and places where people are of Scandinavian and Northern European descent may have particular risk factors for GCA (13), including climate, genetics, and association with HLA-DR4 (14).

Incidence by age:

It is well known that incidence of GCA is much higher in populations over 50 years of age (7,9,13,14,17) and continues to increase with age(11) . Age of onset is between 67 and 78 years and peaks in the 80th decade (7,9,10,13,14,16,17,19). In Japan peak age was much lower between 60 and late 60's (18).

The numbers of people who could be affected by this disease is estimated to double in the next 25 years due to aging populations and the fact that aging itself is a relevant risk factor (20).

Incidence by gender:

The incidence of GCA is overwhelmingly higher in women, with an incidence in women being between 2 and 7 times higher than in men (7,9,12,21).

The difference between genders becomes more accentuated with age (7).

The Minnesota study and Swedish study found that there was an increase in incidence of GCA in the female population, whereas the male population showed decreasing figures (2,15,22). It has been suggested that this indicates a detection bias (7).

Seasonal and Yearly Variations in Incidence:

A reappraisal of the Minnesota study by Salvarani et al 1995 and again in 2004, found a trend in incidences of CGA. It was found that there was a clustering of cases every 5-7 years, suggesting an environmental factor in the development of disease. It has been hypothesised there may be a relationship between ParvoB19 Virus and GCA (22). A seasonal fluctuation was also found in a study in Jerusalem, where peak onset of symptoms was in May and June (12). There were also 3 distinctive peaks noted, 8-10 years apart, over the 25 year study period. However there was no association between the peaks and bacterium or viruses (12). In New Zealand a study found peaks in a ten year period 5 years apart (19). A UK study found diagnosis of both, GCA and PMR, was higher in the summer months. In Australia there was a significant seasonal trend of diagnosis

in the warmer months of December to January (21).

Contrarily, there were no seasonal variations or yearly peaks found in incidence in a 2007 northwest Spain study (10). And in addition a 1999 Study in Sweden found seasonal peaks in the winter months rather than the summer (23).

Polymyalgia Rheumatica:

Polymyalgia Rheumatic is two to three times more common than GCA in the same age group (6). The estimations vary between different studies and show prevalence figures between 1 in 200 to 1 in 30 of people above the age of 50 (2). One suggested explanation for this higher rate is that GCA may be expressed and diagnosed more frequently as PMR, due to diagnosis being made through response to steroid treatment (9).

Whilst there has been a fairly uniform increase in GCA incidence, PMR appears to have remained relatively stable (24). However, a study in the UK showed an increase in incidence of PMR from 6.9 – 9.3 per 10,000 person years between 1990 and 2001, whilst incidence of GCA remained at 2.2 per 10,000 (11).

Etiology:

The exact etiology of the disease remains to be unknown, however studies appear to suggest genetic, intrinsic and extrinsic contributing factors.

Genetic factors:

High incidence rates of GCA in Northern European populations (and those of similar ancestry) compared to others suggest a genetic predisposition. HLA-DRB1 appears to be overrepresented in populations with GCA (2,25). Other genetic polymorphisms found to be associated with increased susceptibility include those in regard to tumour necrosis factor (TNF), intercellular adhesion molecule (ICAM-1), regulated, on activation, normal T-cell expressed and secreted (RANTES), interleukin receptor antagonist (IL-1Ra) and interleukin 6 promoter(2,26,27) . It is still unclear which populations are affected; large patient cohorts from different parts of the globe are still needed to validate relationships (28).

Intrinsic factors:

Ageing appears to be a predominant factor in the genesis of GCA. Very few cases in people under 50 years of age have been identified (26). Degenerative changes in the elastic tissue of arteries may play an important role, leading to the development of antigenic features and causing autoimmune response in susceptible individuals (2). Further possible explanations include the deterioration of immune tolerance (26), a continuous inflammation due to higher cortisol levels related to stress, or reduced resistance against infectious triggers (2).

Additionally, female gender appears to be associated with an increased risk to develop the disease. It is suggested that estrogen may play a role in female susceptibility (26).

Extrinsic factors:

Infections may have a relevant influence, in view of the fact that periodic cyclic fluctuations of GCA cases have been found which in itself may suggest an infectious etiology. In addition, a Danish study discovered these cycles to be synchronized with the peaks of epidemics, such as Mycoplasma pneumonia, chlamydia pneumonia and ParvoB19. A French study inquired the serologic markers for different viruses and found patients with GCA to have 2-3 times higher

likelihood of having IgM antibodies against Parainfluenza Virus type 1 (2). Russo et al 1995 found that patients with GCA were 5 times more likely to have had an infection (varied types) than those without GCA (29). However, no single pathogen has consistently been identified in patient biopsies, indicating there are multiple disease instigators (28).

Pathophysiology/Pathogenesis

The pathophysiology of GCA is yet to be fully understood in all its detail, the following outlines the majority of the currently known pathways and correlations.

In GCA, inflammation primarily affects the proximal aorta and its branches. These large and medium sized muscular arteries have a prominent internal elastic membrane and vasa vasorum. Interestingly, as the arteries become smaller, for example the intracranial arteries, they are rarely affected by this disease. One of the reasons may be that they have less elastic tissue and no vasa vasorum (6).

The clinical manifestation of this disease can be explained by 2 immuno-pathogenic processes. There is a component of systemic inflammation that represents a massive stimulation of the innate immune system. The second process is best described as damage to the artery caused by an abnormal adaptive immune system response, leading to t-cell infiltration of the artery and structural damage(20).

The link between these 2 entities is found through dendritic cells. These cells act as surveillance cells in the tissues and upon recognizing a pathogen; they are activated and normally migrate to a local lymphnode, then present the antigen to the immune cells of the adaptive immune system. In all human arteries with a vasa vasorum, dendritic cells are located at the adventitia media border. Dendritic cells are potent immune activators, but also play an important role in the tissue defence against attack (20). Dendritic cells in blood vessels are essential in defining regionalism in arteries. Immuno-surveillance varies greatly among different regions with arteries from different regions found to have different toll like receptors (30).

In GCA, dendritic cells are activated for an unknown reason (20). In healthy patients they remain immature and play a vital role in maintaining T-cell tolerance of the tissue. This is achieved when dendritic cells and T-cells interact with each other and the dendritic cells send an inhibiting signal to the T-cells. In arterial tissue samples of patients with GCA or PMR, multiple mature dendritic cells can be found (20). The activated dendritic cells produce chemokines which recruit T-cells and macrophages (CCL, 19, 20 and 21), show expression of co-stimulatory factors (CD83, 40, 80, 86) and ensure the persistence of systemic inflammation by secreting cytokines (IL 1beta, IL-6) (31). One special feature found in GCA and PMR is that upon activation dendritic cells do not leave the tissue. This is due to their production of homing chemokines CCL18, 19, 21 in the artery, while at the same time they possess compatible chemokine receptors (CCR7). Producing the lure and the receptor locally means that they are trapped in the artery. Typically these chemokines are produced in lymph nodes. CCL 19 and 21 also attract t-cells and macrophages(32)(19)(31).

The activation of the innate immune system and the loss of self-tolerance seem to be the initial step in the disease progression in GCA (31). As already mentioned, the reason for the loss of self-tolerance is not known. The systemic inflammatory response is mediated by the innate immune system and is an acute phase response typically to stress and injury. Dendritic cells, Monocytes and Macrophages in the inflamed artery and those circulating in the body produce IL-6 and IL 1beta and IL-23. Indirectly, IL-6 is a major contributor to the production of acute phase proteins in the liver (20). High levels of IL-6 are associated with lower risk of ischemic complications (33).

Once the dendritic cells are activated, inflammatory cells enter the blood vessel via the vasa vasorum. This part represents the adaptive response. The entry does not occur via the lumen of the blood vessel itself (20). A main component of the infiltrate are T-cells and macrophages (6,20,28,32). These cells can be found in every layer of the artery. In the adventitia t-cells are stimulated and expand clonally (34). Once activated, they secrete Interferon Gamma, which recruits and regulates the function of macrophages and the granuloma formation in the media (20,32). By examining disease chronicity via repeated temporal artery biopsies and peripheral blood analysis, Deng et al discovered that two T cell lineages are

present in inflamed tissues and that glucocorticoid treatment only suppresses one T cell type (35). Despite optimal glucocorticoid (GC) treatment over 80% of patients were still found to have positive biopsies after 6 months of therapy. Th17 and Th1 cells are part of 2 different pathologic pathways leading to systemic and vascular manifestations. Th17 cells appear to be a vital player in acute systemic and vascular manifestations, whereas Th1 cells are associated with persistent vascular lesions. While GC treatment is able to affect and normalise TH17 numbers, Th1 cells are not affected and continue to uphold chronic vasculitis. Targeting the Th1 population is a necessary task for effectively treating chronic smouldering vessel inflammation (35).

Macrophages:

Upon activation macrophages display a wide array of functions relevant to tissue damage (28). Macrophages can be divided into a M1 and M2 subgroup, where the first are responsible for inflammation and the later induce tissue repair and neoangiogenesis (28). The production of angiogenic growth factors by M2 macrophages and multinucleated giant cells represents the response to injury program and causes maladaptive lumen occlusive intimal hyperplasia (20). The macrophages respond depending on their location. In the adventitia they produce pro-inflammatory cytokines (IL1 and IL6) which are involved in systemic acute phase responses (28). In the smooth muscle layer of the media, M1 macrophages focus on oxidative stress and produce metalloproteinases. The resulting oxidative stress causes injury to the smooth muscle cells and endothelial cells (20,28,32). In the media intima junction the M2 Macrophages produce growth and angiogenic factors such as vascular endothelial growth factor, platelet-derived growth factor and fibroblast growth factor, that leads to intimal hyperplasia(20,28). This demonstrates a strong self-involvement in directing the inflammation by the artery itself. The mechanism of the disease is different to other forms of vasculitis. In GCA the granulomatous inflammation does not lead to necrosis. The lytic enzymes do not typically destroy the arterial wall in GCA, but they do however destroy the elastic intima lamina.

Histology

The artery is made up of 3 major layers. From inside to outside the layers are called the intima, media and adventitia layer. Between the intima and media and between the media and adventitia, elastic laminae can be found, the lamina elastica interna and lamina elastica externa(36) .

Arteries can be differentiated by the predominant components of the medial layer. There are arteries of the elastic type and those of the muscular type. Arteries of the elastic type are found centrally close to the heart whereas muscular vessels are further peripheral (36). See **Figure 1** for demonstration of an uninflamed temporal artery.

Histopathology

The inflammation tends to affect the arteries in a segmental fashion (6). The classical histomorphological finding shows mononuclear cell infiltrates in the adventitia, media and intima (28) (see Figure 2). The infiltrate consists of macrophages and lymphocytes (20). The multinucleated giant cells, that the disease is named after, are found in only 50% of patients (37). When present, these giant cells have the tendency to be located near to the elastic lamina (28). The affected artery typically shows patchy degenerations and dropout of smooth muscle cells in the media intima junction leading to media thinning and a disrupted and fragmented internal lamina (2,28). Occlusion of the artery is caused by intimal hyperplasia (28,32) and partly by edema (2). Migration and outgrowth of myofibroblasts and neo-angiogenesis of capillary networks are found to be precipitating factors of the hyperplasia. Luminal thrombosis can occur (2).

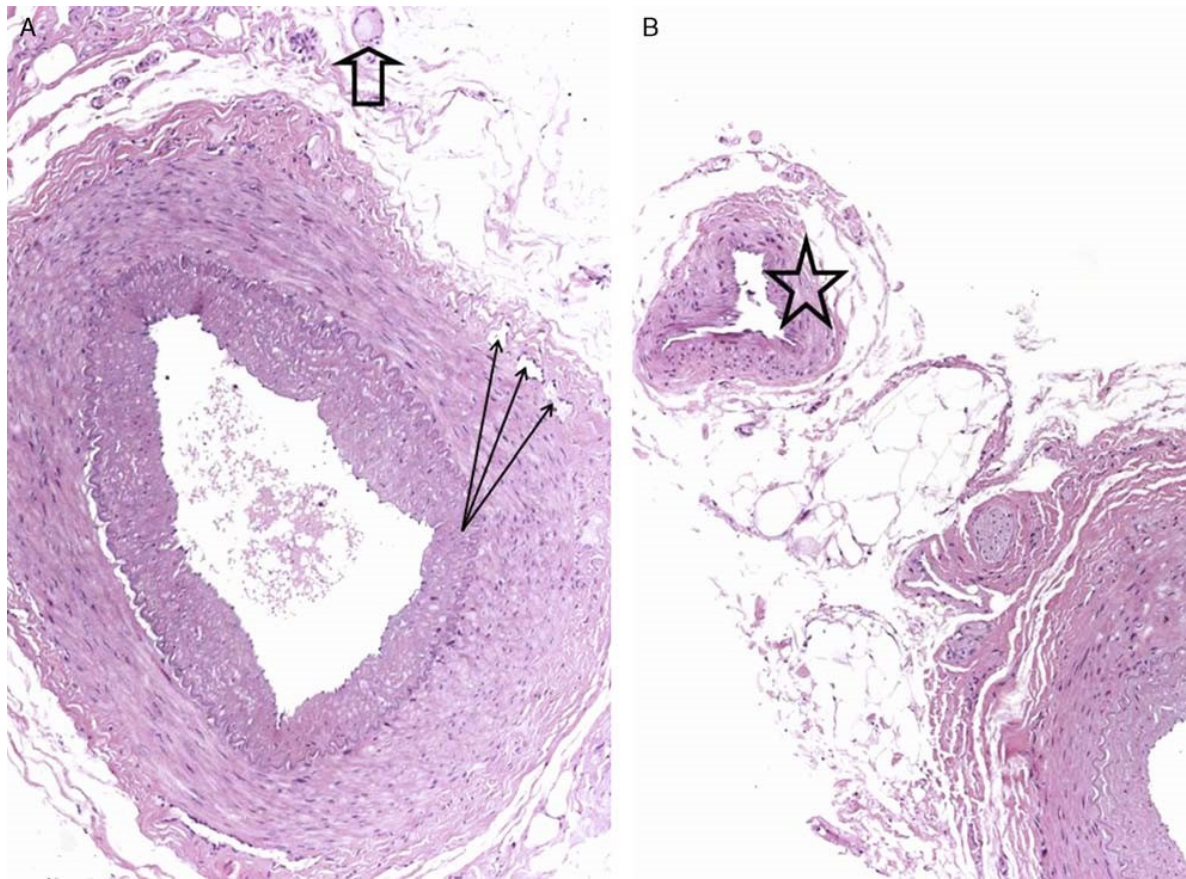


Figure 1: Examples of un-inflamed temporal Artery(38)

Vasa vasorum are localised in the adventitia (arrows), in the periadventitial tissues there are small vessels devoid of muscular coat (arrow head) and small branches with muscular coat (star)" (38)



Figure 2: Classical example of transmurial inflammation of the temporal artery (38)

The inflammatory infiltrate can be limited to different parts of the artery (See Figure 3). Inflammation can be located in the periadventitial small vessels, which lack a muscular coat (38), the process can be limited to the vasa vasorum. There may be sparing of the media and intima (6,20,38), or the infiltrate can be found in all layers (38).

A study conducted in 2014 by Alberto Cavazza found that, in temporal artery biopsies, a wide spectrum of different inflammation types can be found and that these differences in pattern have clinical implications on the symptoms and therapy (38).

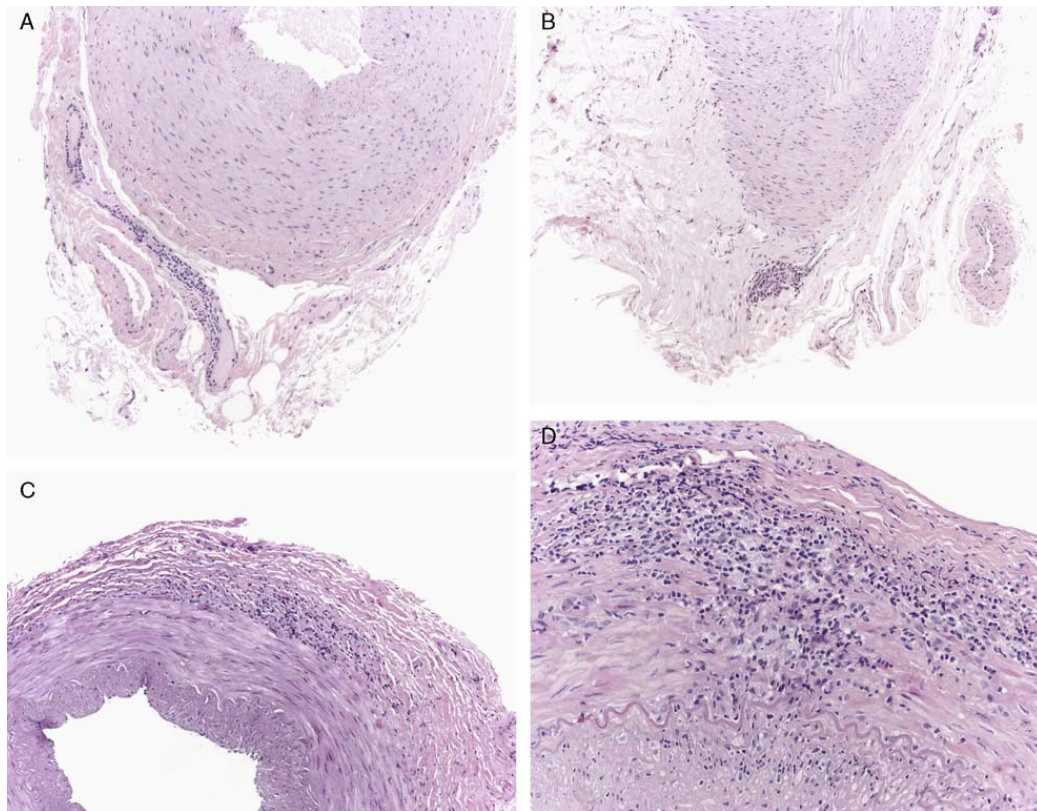


Figure 3: Different patterns of inflammation in the temporal artery (38)

A- inflammatory infiltrate surrounding the periadventitial small vessels, The temporal artery is not affected. B- the inflammatory process is located around the vasa vasorum. C- inflammation of the adventitia, no visible inflammation in the media. D- transmural inflammation (38)

There is the possibility of other diseases manifesting in the temporal artery. Histological manifestations such as fibrinoid necrosis is found rarely in GCA and therefore could serve as a clue for other vasculitides such as panarteritis nodosa and ANCA vasculitis (20,28).

Healed temporal arteritis show medial scarring and neovascularisation. Mild inflammation can be present. The elastic internal lamina remains fragmented, and irregularly arranged fibrous tissue can be found in the intima (2).

GCA affecting the aorta causes aortitis. The aortic wall is mildly thickened. The inflammatory infiltrate can be transmural, but seems to be dominantly multifocal in the media layer. The cells are mostly lymphoplasmocytic or lymphohistiocytic (see **Figure 4**). Giant cells can be regularly identified at the borders of necrotic zones of laminar necrosis. Laminar medial necrosis is frequently present as well as medial degeneration and intimal arteriosclerosis. It should be noted that medial degeneration and arteriosclerosis are common findings in elderly patients like GCA patients and are not caused by the disease itself (39). Smooth muscle cells positive for alpha smooth muscle actin are largely reduced in the media in non-inflamed areas. Multiple acellular calcified lesions can also be found in the medial layer. Petursdottir suggests that loss of smooth muscle cells is primary and that the inflammatory reaction is secondary. The atrophic media tissue appears to be the trigger for inflammation (40). Chronic aortitis shows chronic inflammation and secondary intimal fibroplasia and adventitial fibrosis. Histological distinction between isolated aortitis, GCA aortitis and rheumatoid arthritis aortitis is not possible (39).

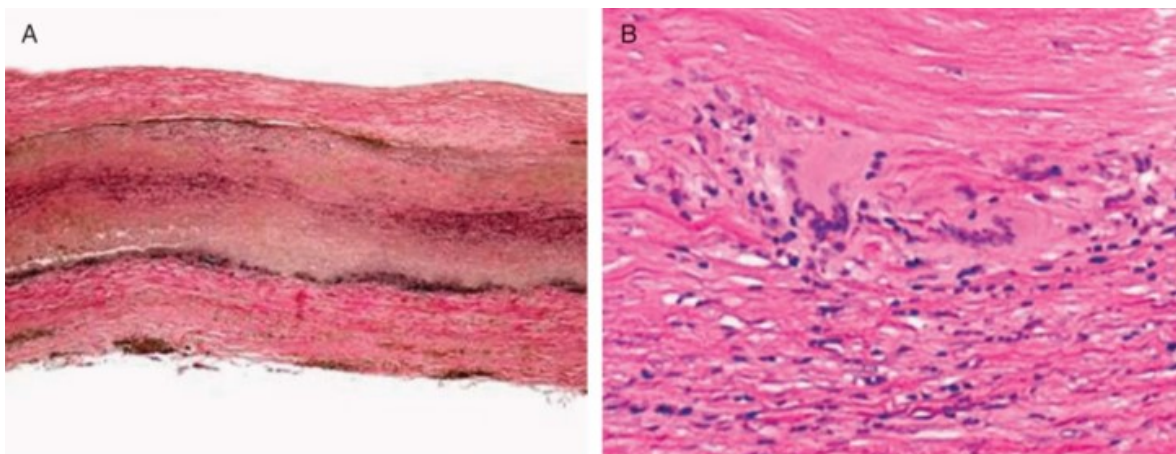


Figure 4: GCA aortitis (39)

A- inflamed aorta showing transmural medial destruction and replacement by lymphohistiocytic inflammation. B- magnification of A, showing multinucleated giant cells (38).

Histopathology of Polymyalgia Rheumatica

Muscle biopsy can show signs of atrophy but no myositis (41). Biopsies of affected joint can reveal low grade synovitis (42). Nordborg et al described that patients with non-inflamed arteries showed significant non-reactive media atrophy in comparison with controls and the internal elastic lamina had significantly larger calcifications (43).

Clinical presentation

Giant Cell Arteritis:

The clinical findings in GCA can be separated into 2 different groups. The symptoms can be separated into vascular and extravascular components.

Vascular:

Vascular GCA can again be divided into cranial arteritis, which mainly affects the external carotid artery, and large vessel arteritis, predominantly localised in the aorta and its upper extremity branches (20).

The clinical features of cranial GCA can be explained by vascular insufficiency of the branching arteries of the external carotid artery. These findings are scalp tenderness, headaches, occipital tenderness, tongue- and jaw claudication. New onset headaches are present in 2 of 3 patients (6), they are very intense and often don't respond properly to analgesics (20). The pain is typically localised over the temporal or occipital areas (6). The claudication can be triggered by chewing dense food or even talking (28). The frontal and parietal branches of the superficial temporal arteries can be thickened, nodular, tender, erythematous, and have decreased or absent pulses (6). Jaw claudication was found to have a strong predictive value for GCA (44) and rarely arises outside of this disease.

An early and one of the most serious manifestations of the disease is permanent partial or complete blindness, affecting up to 20% of the patients (45,46). The loss of vision is again caused by narrowing or occlusion of smaller arteries, causing ischemia anywhere along the visual pathway (20), but commonly affects the ophthalmic artery (28) or the posterior ciliary arteries (6). Early fundoscopy may reveal slight pallor and edema of the optic disc, small haemorrhages and cotton

wool patches (6). Later findings show optic atrophy. The vision loss is sudden, painless, can affect one or both eyes and once established, visual impairment is permanent. If untreated the second eye is likely to become affected within 1 or 2 weeks (6). The early morning hours are a high risk period (28). Patients can develop symptoms such as amaurosis fugax or diplopia before suffering from permanent loss of vision (20). This makes GCA an ophthalmic emergency (28).

Inflammation of the vertebral or basilar artery can cause transitory ischemic attacks or even stroke (28). Zenone et al found that 6.1% of patients in their study cohort had cerebrovascular accidents at time of diagnosis (47). Once therapy was induced, no further occurrences of cerebrovascular events were detected. This suggests that TIA or stroke might be an initial manifestation of GCA (47). Comorbidities such as hypertension, past history of ischaemic heart disease and low inflammatory response contribute to a higher risk of developing cranial ischaemic events (6). GCA should be considered a potential diagnosis in an elderly patient with stroke and unexplained elevation of inflammatory markers (47).

Large vessel arteritis is a manifestation of GCA, which can occur without the classical symptoms of cranial arteritis and with lesser or no systemic inflammatory symptoms (48). It is estimated that 50% of patients with GCA of the subclavian or axillary arteries have negative temporal artery biopsy results (49). Up to 27% of GCA patients have large artery complications (48). Apart from the aorta, the other blood vessels upon inflammation have the tendency to occlude and thereby cause symptoms of ischemia. The vessels potentially involved are primarily the aorta, the subclavian arteries, the axillary arteries, the vertebral arteries and in some cases the carotid or lower extremity arteries can be involved (28). Clinical findings can be summed up into the definition of aortic arch syndrome, which occurs in 10-15% of patients with GCA (6). It consists of bruits over the affected arteries, asymmetric blood pressure, diminished or absent pulses (48,49). Hypoperfusion of the extremities can rarely lead to necrosis but more often causes bluish discoloration and painful hands are frequently described. Ischemic pain in the affected extremity is triggered by physical activity (28). In some patients with these symptoms it is more difficult to differentiate between vasculitis and atherosclerosis as both diseases manifest in the elderly (28).

Aortitis is the most serious complication of GCA (50) and is doubtless under-diagnosed (48). The entire aorta can be affected, but the majority of complications affect the thoracic aorta (20). Rather than stenosis, inflammation of the aorta causes dilatation and aneurysmal formation (48). This is caused by progressive destruction of the vessel wall integrity (28). Aortitis is frequently clinical silent until signs and symptoms of dissection occur. These consist of chest pain, shortness of breath, lack of pulse and hypotension caused by aortic rupture or aortic valve insufficiency (48). Though presumably present upon diagnosis, (50) aortitis may be asymptomatic and manifest much later in the disease when an aneurysm is incidentally diagnosed or when dissection appears (51). The risk of developing aortic aneurysm or dilatation is substantial (22% of 54 GCA cohort) in GCA patients (52). Thoracic aneurysms are 13 times more likely to occur in GCA than in healthy control groups (6).

Some rare symptoms make initial diagnosis more difficult. Respiratory tract symptoms such as dry cough occur in approximately 10% of patients (53). Zenone et al conclude that GCA should be considered as a differential diagnosis in elderly patients with unexplained elevation of inflammatory markers and chronic dry cough(53). Other rare manifestations can be scalp necrosis, ulceration and infarction of the tongue, pericardial and pleural effusions, female genital tract of breast involvement, syndrome of inappropriate antidiuretic hormone secretion and dysarthria (6).

Extravascular giant cell arteritis

In vascular giant cell arteritis systemic symptoms can be the only presenting symptom even though the arteries show inflammatory infiltrates in the biopsy.

Most patients are affected by one or more systemic manifestations (6), often reminiscent of malignancy associated failure to thrive (20). Fever, weight loss, night sweats, malaise and depression can prompt patients to be examined for an unrecognized malignancy (28). Fever is typically low grade but can reach up to 39-40 degrees Celsius in up to 15% of patients and might be the presenting or even only feature of GCA (6,54). Therefore GCA can present as fever of unknown origin (FUO) in 15% of patients. Only 2 % of all FUO cases are caused by GCA,

but in the age group above 65 years GCA contributes to up to 16% (55). In the subset of patients only presenting with systemic symptoms and no or few other signs, temporal artery biopsy should be considered in the work up to identify underlying GCA. In this group of patients the artery may upon inspection not appear to be tender or swollen and the histological picture might show inflammation without hyperplasia and luminal occlusion.

Polymyalgia Rheumatica

Looking at the current research and at all known factors of these 2 entities, there are strong indications that PMR is an atypical or attenuated form of GCA. PMR can be described as GCA with a dominant extravascular and an incompletely developed vascular component (28). About 40% of GCA patients have PMR and about 10% of patients originally presenting with isolated PMR have GCA positive temporal artery biopsies (20). The occurrence of high ESR and systemic manifestations in PMR predicts the presence of silent GCA(6). Typical symptoms include intense pain and stiffness of the neck, shoulder and pelvic girdle muscles, sometimes the torso and almost never affecting the forearms, hands and peripheral legs (28). The pain is commonly described to radiate distally into the knees or elbows. It can start unilateral but typically proceeds to affect both sides. Movement appears to trigger the worst pain and patients often describe to have an issue with sleeping(6). Upon examination a painful reduced active and passive movement radius in the shoulder and hip joints can be seen. Forty percent of PMR patients experience systemic symptoms such as low-grade fever, depression, fatigue and weight loss (6). Fever of high and spiking character are uncommon in PMR without presence of arteritis (55). Distal musculoskeletal manifestations such as carpal tunnel syndrome, diffuse swelling of the distal extremities with pitting oedema and non-erosive, self-limiting peripheral arthritis, occur in approximately half of the patients (6). Eight to twelve percent of PMR patients develop swelling and pitting edema of the hands or feet. These symptoms are similar to those found in remitting seronegative symmetric synovitis with pitting edema syndrome. In PMR, these findings promptly remit to small doses of GCs and typically manifest unilaterally and predominantly on the dorsum of the hand (6). Kreiner et al recently measured cytokine abnormalities in symptomatic

muscles, he showed, that the muscle rather than the joint might be the primary site of inflammation in PMR (56).

Diagnostics:

Classification of GCA

American College Rheumatology:

In 1990 the American College of Rheumatology (ACR) introduced a 5 point classification criteria with the purpose to identify and discriminate GCA in patients with 7 types of Vasculitis (57,58). These criteria are often falsely used for diagnosing GCA in individual patients. In 1998 Rao et al demonstrated that the 1990 criteria perform poorly in the diagnosis of specific vasculitis (57).

1990 Criteria for the Classification of Giant Cell (Temporal) Arteritis - Excerpt(58)

1. *Age at disease onset ≥ 50 years:*
Development of symptoms or findings beginning at age 50 or older
2. *New headache:*
New onset of or new type of localized pain in the head
3. *Temporal artery abnormality:*
Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
4. *Elevated erythrocyte sedimentation rate:*
Erythrocyte sedimentation rate ≥ 50 mm/hour by the Westergren method
5. *Abnormal artery biopsy:*
Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

There are several diagnostic procedures that can be applied to GCA patients, but temporal artery biopsy remains the gold standard for diagnosis (6).

Temporal Artery Biopsy:

When making the decision to perform an invasive procedure and whether to start glucocorticoid treatment early in order to prevent serious disease complications, the clinician is faced with a wide range of clinical and historical presentations in patients. Smetana et al found that of historical details, only jaw claudication and diplopia increased the likelihood of finding temporal arteritis in the biopsy (44). A clinical factor that reduces the likelihood of having a negative biopsy is the absence of any temporal artery abnormality, whereas beading, prominence and tenderness of the temporal artery increase the probability of GCA. Younge et al found that jaw claudication alone and in combination with other symptoms has a strong positive predictive value (59). The most useful finding attributing to unlikelihood of GCA is a normal ESR (44).

The histological features found in GCA have been already described in the section of histopathology.

Temporal artery (TA) biopsy is commonly performed by vascular surgeons (60). Apart from the temporal artery, other arterial sites such as the occipital artery are rarely biopsied. Some GCA cases are occasionally found during aortic aneurysm surgery (28).

Most of the TA biopsies are managed in an outpatient setting. During this procedure a sample of approximately 2-3 cm is taken. Considering the fact that the vasculitis can occur in skipped lesions, longer segments of the arterial biopsy improve the chance of finding vasculitic infiltrates (28). During this procedure several complications such as unintended biopsies of veins and nerves, postoperative haematoma, scalp necrosis, wound infection, damage to the facial nerve and drooping of the eyebrow can occur (60). One sided biopsy has a 97% diagnostic efficiency and double sided biopsy only improves the diagnostic yield in 3% of patients. (61). Bilateral biopsy offers little additional diagnostic information and therefore is not routinely recommended. (28).

Treatment of patients with GCs before biopsy is a crucial question. Vascular lesions seem to be rather resistant to therapy (20). Narvaez et al found that TA

biopsy is valuable for up to 4 weeks after initiation of high dose GCs, they therefore conclude that therapy should not be withheld (62).

Laboratory findings

Routine laboratory tests are useful to detect haematological and biochemical changes present in GCA and are representative of the acute phase response. These include the presence of anaemia, which is typically hypo- or normochromic, normocytic, thrombocytosis and alkaline phosphatase elevation (28). Interestingly anaemia was found to be a negative predictor for ischaemic complications in GCA (63). The acute phase response is efficiently framed by elevated ESR and CRP (28). The levels described in the 1990 classification state an ESR over 50mm/h (58), but cases with lower levels occur (6). CRP is less affected by external factors and so is presumed to be a more sensitive indicator of disease activity (6).

Other acute phase proteins are fibrinogen, serum amyloid and alpha-macroglobulin and can also be useful to determine disease activity (28). Interleukin 6 (IL-6) is the most sensitive marker to examine innate immune activation, but is not frequently available in most laboratories (6); furthermore, IL-6 was found to correlate closely to CRP measurements (64).

Laboratory biomarkers such as ESR and CRP are not sufficient to make a diagnosis but are useful for monitoring disease activity and treatment response. There is the possibility of these parameters being normal even before treatment. This leads to the conclusion that a missing acute phase response is not enough to withdraw from the diagnosis of GCA (20).

Rheuma factor and ANCA are usually negative (6), but when positive, these parameters can be used to identify mimicking diseases (28).

Imaging Studies

For the diagnosis and monitoring of aortitis and vasculitis of aortic branch arteries, modern imaging modalities are important and often the only diagnostic tools (28). Imaging is useful in large vessel vasculitis and medium vessel vasculitis, but is unable to visualize small vessels (65). The main imaging tools used are Colour

Doppler Sonography (CDS), magnetic resonance imaging (MR), computer tomography (CT) and positron emission tomography (PET)(65).

Ultrasound:

CDS is increasingly used for suspected GCA. Its limited cost, higher resolution than MR, fast image requisition and lack of radiation make it favourable (65). Typical findings include hypoechogenic concentric wall thickening, also known as halo sign, stenosis and occlusion of the blood vessel (65). The sensitivity of CDS and the access to the temporal artery have led to questioning if this method would be a viable replacement to temporal artery biopsy (28). Current meta-analysis showed that upon scanning the temporal artery for GCA, the presence of a halo has a sensitivity of 75% and a specificity of 83% when using histological criteria for reference standard (66) and a sensitivity of 68% and specificity of 91% using the 1990 ACR criteria (67). When halo signs are present the specificity is up to 100% (67). CDS can also be used to examine the large arteries for halo signs, aneurysm and stenosis (65). The vessel wall thickening persists even after successful therapy, but the halo sign resolves after a time period between 1-32 weeks (68,69). This leads to a decrease in sensitivity and specificity after initiating glucocorticoid treatment (70). Limitations of this method are problems with the visualisation of the thoracic and abdominal aorta and a substantial degree of operator dependency (65).

CT and CT angiography

CT is especially effective in the detection of inflammatory changes in deep, large arteries such as the aorta (71). CT shows typical early changes in the affected vessel including wall thickening and mural enhancement. CT-Angiography is useful in detecting large vessel complications, such as stenosis or obstruction (65). The biggest disadvantage of these 2 methods is the exposure to radiation, which limits repeated CT-studies (71). An advantage over magnetic resonance (MR) consists in the shorter duration of the procedure, which caters towards claustrophobic patients (28).

MR and MR angiography

The strongpoints of these 2 methods are similar to those of CT and CT-angiography for the detection of GCA in large arteries (65). The findings depends

on the weighting and can be increased thickness of the arterial wall, with a diffuse pattern, associated with edema of the vessel wall (T2 fat suppressed sequence) or mural enhancement (T1 sequence) (72,73). MR is also affected by GC therapy, where inflammatory enhancement significantly decreases under treatment (74).

¹⁸-F-Fluorodeoxyglucose Positron Emission Tomography

Advantages of PET are the visualisation of almost all large arteries except the renal and temporal artery and in comparison to CT, the small dose of radiation (65). PET evaluates the degree of vascular uptake of radiolabeled glucose analogue by activated inflammatory cells in infections, malignancies and inflammatory processes (71). The uptake intensity in large vessels is typically graded on a semiquantitative 4 point scale. (0=none, 1=less than liver uptake, 2=similar to liver uptake, 3=higher than liver uptake). Grade 1 and 2 are specific for vasculitis (75). In a study where international experts were asked to diagnose and determine clinical management in patients with suspected large vessel vasculitis by adding or excluding the use of PET, PET increased the diagnostic accuracy from 54% to 71% (76). This shows that PET significantly improves the diagnostic accuracy in patients with large vessel vasculitis (76). Treatment with immunosuppressive drugs proved to dramatically decline the accuracy of diagnosis by nearly 50% (76). Problems include the limited availability, the high costs and not being able to show morphologic details in the vessel wall and lumen (71).

Classification of PMR:

Polymyalgia rheumatic is diagnosed on a combination of clinical symptoms, described in clinical manifestation, raised acute phase reactants identical to GCA, the exclusion of other diseases especially GCA and response to glucocorticoids (77).

Table 2 shows three commonly used criteria used for diagnosis of PMR.

Diagnostic Criteria for Polymyalgia Rheumatica

Chuang et al 1982

- 1** Patients 50 years or older
- 2** Bilateral aching and stiffness persisting for 1 month or more involving two of the following areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs
- 3** ESR greater than 40 mm/h
- 4** Exclusion of other diagnoses except giant-cell arteritis

The presence of all these criteria defines diagnosis of polymyalgia rheumatica.

Healey 1984

- 1** Persistent pain (for at least 1 month) involving two of the following areas: neck, shoulders, and pelvic girdle
- 2** Morning stiffness lasting more than 1 h
- 3** Rapid response to prednisone (≤ 20 mg/day)
- 4** Absence of other diseases capable of causing the musculoskeletal symptoms
- 5** Age over 50 years
- 6** ESR greater than 40 mm/h

The diagnosis of polymyalgia rheumatica is made if all the above criteria are satisfied.

Bird et al 1979

- 1** Bilateral shoulder pain and/or stiffness
- 2** Onset of illness within 2 weeks
- 3** Initial ESR higher than 40 mm/h
- 4** Morning stiffness exceeding 1 h
- 5** Age older than 65 years
- 6** Depression and/or loss of weight
- 7** Bilateral upper arm tenderness

A diagnosis of probable polymyalgia rheumatica is made if any three or more of these criteria are fulfilled. The presence of any three or more criteria yields a sensitivity of 92% and a specificity of 80%.

Table 1: Diagnostic Criteria for Polymyalgia Rheumatica (77)

Therapy

Pharmacological therapy is proven to be very effective against systemic manifestations, but its effects on the vessel inflammation are less known (28).

Glucocorticoids:

As the therapy of choice, glucocorticoids (GC) are fast acting and effective in inhibiting clinical manifestations and ischaemic complications (77). The effects lie particularly in the suppression of the extravascular component (20). Interestingly, prompt response to glucocorticoid treatment is part of the diseases entity and in patients, improvement of headaches, malaise, fever and PMR can be observed within 24-48 hours (28). Upon initiation of therapy, the severity of disease, including impending ischaemic complications, have to be evaluated. Usually, when no ischemic complication is noted, oral prednisone at doses of 1mg/kg is administered and under monitoring continued for 3-4 weeks (28). In case of visual loss or other signs of vascular complications related to GCA, 3 days intravenous (IV) pulse therapy with 500-1000mg methylprednisolone is recommended. Following the IV therapy, oral GCs are commenced. After 2-4 weeks, once the clinical symptoms are under control and acute phase reactants (typically ESR and CRP) normalised, GC dosing can be tapered (6,28). Close monitoring of any form of disease symptom or complication is important (28). The dose reduction is individual from patient to patient, dependent on clinical response, decrease of inflammatory parameters and potential side effects of steroid treatment. According to literature reports, decreasing the initial dose by 10-20% every 2 weeks is a practicable way to reduce side effects of steroid treatment (6,28). Upon reaching 10mg/day, tapering should be slowed to a rate of 1-2mg every 4 weeks (28). The duration of treatment is variable, but in most cases steroids can be discontinued after 1-2 years (6). Over 80% of patients will experience at least one disease flare. Therefore careful clinical monitoring through clinical examination and laboratory tests are necessary. Once present, the flares are usually suppressed by increasing the steroid dosage slightly. Occurrence of disease complications during treatment should lead to prompt initiation of pulse therapy (28). Mazlumzadeh et al demonstrated that initial IV methylprednisone pulse therapy in comparison to

only taking oral GCs, has several benefits, such as faster tapering, less flares and a higher rate of remission (78).

As the pathogenesis is becoming better understood, there is evidence that at least in some patients the disease is not self-limiting and that smouldering vasculitis persists, despite optimal GC therapy (28). There are at least two different T cell lineages involved in the inflammation and it has been shown that unlike Th17 cells, Th1 cells are unaffected by GCs. This leads to the conclusion that a combination of therapies is needed to fully control the disease including the vessel wall inflammation (79).

Patients should be regularly monitored for signs of large vessel inflammation such as aortic involvement (28). Long term glucocorticoid therapy commonly has adverse effects (6). Primary determining factors for side effects are the patient age and the cumulative dose. Proven et al found that in their patient cohort 86% developed adverse effects and that 58% experienced 2 or more side effects (80). Adverse effects were defined as diabetes mellitus, bone fractures, gastrointestinal bleeding, hypertension, infection and cataract. The study concludes that less toxic therapeutic strategies are needed (80).

Adjuvant therapy

To minimize GC side effects all patients should receive vitamin D (800 IU/day), calcium (1000-1500mg/day) and Biphosphonate therapy should be given when reduced bone mineral density with a T-score less than -1SD is present (6). When patients are started on glucocorticoid treatment, bone density measurements should be made and when normal repeated every 12 months (81).

Methotrexate:

The numerous side effects of GC therapy have led to inquiry into the effect of steroid sparing immunosuppressive drugs on GCA (6). So far little evidence exists (28). Mahr et al provided some results showing that adjunctive low dose methotrexate is beneficial, but only in female patients under 75 years of age. Another problem is that an effect was only seen in treatment periods longer than 48 weeks (82). Salvarani et al don't recommend the use of methotrexate on a routine basis, but suggest a possible benefit in patients at severe risk of GC side effects (6).

Aspirin:

Aspirin is widely recommended to be added to therapy for its anti-platelet and anti-inflammatory properties (6,20,28). Studies on mice showed that aspirin suppresses Interferon gamma, which plays a crucial role in early and late disease (83). Salvarani et al recommend when treating with GCs and Aspirin to add proton pump inhibitors (6).

Surgical options:

Procedures such as stenting, bypass procedures or aortic root repair can become necessary, when acute complications arise. Even though due to severe acuteness not always possible, optimal disease control is generally sought after before performing these procedures. Active vasculitis can complicate surgery results through rapid restenosis and compromised flow at insertion sites (28).

Tocilizumab:

The blockade of IL-6 leads to a decrease of Th17 differentiation in the T-cell population and thereby helps to suppress the acute vascular and systemic manifestations (84). Tocilizumab, a humanised monoclonal antibody against IL-6 receptors, found to be an effective therapy option for patients with poor disease control despite optimal GC therapy and is thought to be a beneficial source for rapid remission (84-86).

Prognosis and Complications

Prognosis

A literature review conducted in 2014 found that giant cell arteritis generally presents a good prognosis with a mortality rate similar to that of age matched controls (87). However, GCA is associated with significant morbidity with some patients developing visual loss, peripheral neuropathies, scalp necrosis, altered mental status, congestive heart failure, myocardial infarction, aortitis, aortic aneurysm and stroke (37,88) .

Whilst prognosis is good, there is evidence of increased frequency of potentially fatal events, such as myocardial infarctions and cerebrovascular events, particularly in the early stages of the disease (37).

Complications

Complications of GCA are vision loss (usually presenting early in diagnosis), cerebrovascular accidents, aortic aneurysm and aortic dissection (6). The incidence of large vessel manifestations such as large artery stenosis, aortic aneurysm, or aortic dissection is estimated at 30.5 events per 100 person years (89). Patients with GCA were supposed to have a 17 fold increase risk of developing thoracic aortic aneurysm (90). Recent data suggest that this risk might be overestimated.(91)

Mortality

The primary causes of mortality in GCA are cerebral arteritis, coronary arteritis, aortic aneurysms and thromboembolic events (88). There are differing results in the literature as to whether GCA has a negative effect on mortality compared to the general population. Some studies have found GCA to decrease survivorship among patients, particularly within the first 5 years of diagnosis. However, others were not able to show a difference in survival between GCA patients and aged matched controls.

Crow et al did a comparative analysis of 17 studies on mortality outcomes for patients with GCA. Only 7 of those showed an increase in mortality, and two only showed an increase for women, 2 others showed an increase at 5 years, but not at 10 to 15 years, where the age and sex controls converged (88). The apparent disagreement between studies on mortality outcomes may be due to small sample sizes, differing diagnostic criteria for inclusion or a prospective versus retrospective design. Nordborg et al 1989 demonstrated that patients with GCA have increased mortality risk in the initial phase of the disease. However, once treated with GCs, GCA patients have the same risk of death as the general population (92).

It appears there may be a subset of patients, who develop aortic dissections or aortic aneurysms, and that these patients have a higher incidence of cardiovascular and pulmonary death and decreased survival compared to the general population (87,93). Neunninghoff et al found that there was no difference between GCA patients with large artery complications and those without, or against the general population (94). However, patients that developed thoracic aortic dissections had increased mortality- with a survival of only 1.1 years (94).

Mortality is further examined in the discussion of this study, but the effect of GC treatment on mortality is not discussed. There are conflicting results in the literature as to whether long term use of GCs actually contributes negatively to mortality outcomes for patients.

Hachulla et al found that GC treatment induced death as much or more than the GCA itself. The authors found that survival was dependent on the dose of GCs at 6 months, with better survival for patients receiving under 10mg/day of GCs (95).

Nesher et al analysed steroid related complications for patients with GCA and found that 58% of their study group developed major steroid related complications. This was particularly apparent for elderly patients (>75 years), and with those taking steroid doses >40mg/day. The overall standardised mortality ratio of the group was 2.12 (95% CI 1.27-2.96), indicating a significant effect of steroid use on mortality in this patient group (96).

A review of corticoid steroid complications carried out by Pipitone and colleagues found that GC therapy has significant impact on morbidity and mortality outcomes. Common complications include bone fractures, diabetes, infections, congestive heart failure, hypertension, gastro-intestinal haemorrhage and posterior subcapsular cataract (45). The effects were related to the age of the patient and GC dosage. Currently, there is no alternative treatment to GCs for GCA. Therefore the recommendation is tailored prescription and tapering as soon as possible (45).

Aim

The aim of this study is to analyse the mortality of a group of GCA patients treated in the division of Angiology of the department of internal medicine, Medical University of Graz. An additional goal is to investigate a possible connection between aortic aneurysms and mortality.

Methods

Data Collection

The patient collective consists of all consecutive patients at the division of Angiology of the Medical University Graz who have been diagnosed with giant cell arteritis and have a date of diagnosis between 1995 and December 2012. A retrospective analysis of the patient data examined diagnostic factors (biopsy, PET scan, ultrasound parameters), risk factors (gender, hypertension, diabetes mellitus, hyperlipidemia, smoking status), adverse events (coronary heart disease, stroke, heart attack, peripheral arterial disease, ocular manifestations), adjuvant therapy (insulin, metformin, statins, beta blockers, calcium channel antagonists, aspirin, oral anticoagulation) and death (death, cause of death, date of death). An additional focus was to determine the presence of aneurysms and their potential impact on patient survival.

The primary data collection was achieved through retrospective analysis of the electronic and hard copy patient folders. In case of missing data, patients or their treating general practitioners were contacted by phone by a study responsible. The patients and general practitioners were informed about the study and data acquired through this procedure was only used when consent from the patient or GP was given.

Inclusion criteria:

The main inclusion criterion was the diagnosis of GCA with the date of diagnosis 3 years prior to the initiation into the study. We agreed not to restrict the diagnosis of

GCA to biopsy proven events. Therefore diagnosis of GCA was made according to criteria previously published by Chatelain and colleagues. This criteria pathway consists of 9 points (Table 3). Diagnosis of GCA was made if patients were scored the first 3 points and additionally either the 4th point or met two of the points from criteria 5-9. The Criteria can be seen in Table 2

Point	Parameter	Criteria
1	Age	Above 50
2	ESR	Over 40 mm/hour
3	Clinical improvement	72 hours post GC therapy
4	TA biopsy	Positive
5	Clinical abnormal temporal artery	Nodules, thickening, redness
6	Visual symptoms	Amaurosis, diplopia
7	Jaw claudication	Present
8	Headache, temporal or facial pain	Present
9	Signs of systemic inflammation	Fever, weight-loss of 10% within 3 month, general malaise

Table 2- Criteria for GCA diagnosis

Exclusion criteria:

There were no exclusion criteria affecting the patient collective.

Follow up:

The study endpoint and date for follow up were chosen to be December 2012. All patients still alive at this date were counted not to be deceased in the data analysis.

Ethics Approval

The Institutional Review Board of the Medical University of Graz, Austria approved the study.

Statistical Analysis

Parametric data are given as mean \pm SD, chi squared analysis was used to compare mean value and frequency in the case of normally distributed groups, confirmed by Kolmogorov-Smirnov test.

Data is presented as number of patients and percentage unless otherwise stated. Chi squared analysis and Fishers test were to compare frequency of mortality between groups. Statistical significance was assumed for p values<0.05.

Statistics were assessed with IBM SPSS version 22.0

Results

Patient Characteristics

In all, 177 patients participated in this study, 9 were excluded due to uncertainty on diagnosis, and 10 were further excluded due to uncertainty on mortality status. The final study population was 158 patients. There were 112 (70.9%) females and 46 (29.1%) males, the ratio of female to male in our cohort was 2.4:1.

The average age in years at diagnosis was 71.4 (SD ±9.5).

Ninety-nine (62.7%) patients were diagnosed with GCA only, and 59 (37.3%) had GCA with additional symptoms of PMR. Patient characteristics can be seen in Table 3.

n=158	n (%)
Male	46 (29.1)
Female	112 (70.9)
Ratio F:M	2.4:1
Age at diagnosis (mean ± SD)	71.35 ± 9.528
GCA	99 (62.7)
GCA+PMR	59 (37.3)

Table 3- Study Group Characteristics

GCA patients within our study frequently had concurrent mortality risk factors at time of GCA diagnosis. One-hundred and twenty one patients (76.6%) had preexisting hypertension, 31 (19.7%) had diabetes mellitus, 64 (40.5%) had hyperlipidaemia, 12 (7.6%) were smokers and 26 (16.5%) were ex-smokers.

Many patients in the group were also on adjuvant therapies. Sixty-nine patients (43.7%) were on beta-blockers, 53 (33.5%) took ACE-inhibitors, 19 (12%) had calcium channel antagonists, 7 (4.4%) were on insulin, 6 (3.8%) were taking metformin, 83 (52.5%) were taking aspirin (100mg daily), 50 (31.6%) received statins, and 26 (16.5%) were on oral anti-coagulation with vitamin K antagonists.

The average time till follow up was 82 months (\pm SD 29)

All-Cause Mortality

Of the 158 patients being eligible for statistical analysis, 38 patients (24.1%) died within the observational period. The crude mortality rate in the patient group is 1.41% per year. The mean age at death was 80.53 (SD \pm 6.7) years. There were 4 early deaths, defined as death less than 6 weeks post diagnosis, and 32 late deaths, post 6 weeks diagnosis. There was a higher occurrence of death in the patients with GCA versus those with additional symptoms of PMR ($p=0.046$). Of the patients with GCA alone, 29 (76.3%) died, of those with GCA and PMR only 9 (23.7%) died.

Causes of death were 3 strokes, 2 heart attacks, 7 cancers, 3 infections, 3 haemorrhages, 1 suicide, 4 heart failures, 1 thromboembolism and in 14 cases the cause of death was not able to be determined due to lack of records or access to information.

Patients with an older age at diagnosis appeared to have poorer mortality outcomes ($p=0.023$). The average age at GCA diagnosis of patients still alive at time of follow up was 69.23 (SD \pm 9.298) years whilst the deceased group had an average age of diagnosis of 77.96 (SD \pm 6.920) years.

Table 4 shows the mortality outcomes for the study group.

Risk Factors and Mortality

There was no statistical significance between hypertension, diabetes, hyperlipidaemia, smoking or being an ex-smoker and mortality in these groups.

Complications and Mortality

Of the deceased patients, 11 (28.9%) had a previous history of CAD, 4 (10.5%) had peripheral arterial occlusive disease, 3 (7.9%) had amaurosis and 5 (13.1%) patients had a neoplasm prior to diagnosis. None of these factors was found to be significantly related to mortality in GCA patients.

Positive history of stroke (n=19) was significantly associated with mortality (p=0.001). In addition, ocular manifestations (n=48) and ischemic optic neuropathy were further associated with mortality (p<0.001, p<0.001) with 63.2% of deaths within these groups.

Data on heart attack post diagnosis and stroke post diagnosis was only collected for 75 subjects of the patient group. Of these patients 6 (7.9%) had a heart attack, and 11 (14.4%) had a stroke; neither of these factors was significantly related to mortality.

Drug Treatment and Mortality

Information was collected on use of beta-blockers, ACE inhibitors, calcium antagonists, insulin, metformin, statins, aspirin and oral anticoagulation. Of these, only statin use was significantly related to mortality (p=0.017). Of the patients on statins (n=50), 44 (88.0%) patients were alive and 6 (12.0%) were deceased. Of those patients not taking statins (n=108), 76 (70.4%) were living and 32 (29.6%) were deceased at time of follow up.

Biopsy and Mortality

Those patients who had their diagnosis confirmed by biopsy were more likely to be deceased than those who had a negative biopsy, but were diagnosed by other classification (p=0.001). Those with positive biopsy represented 27 (71.1%) of the deceased patient group whilst of those with negative biopsy only 11 (28.9%) were deceased.

Aortic Aneurysm and Mortality

In our patient group no incidence of aortic aneurysm as cause of death was reported.

	Living n(%)	Deceased n (%)	Total (%)	Sign.
Age at diagnosis (years)(mean + SD)	69.23(±9.298)	77.95(±6.920)	71.35(±9.528)	0.023
Male	31(25.8)	15(39.5)	46(29.1)	
Female	89(74.2)	23(60.5)	112(70.9)	0.107
GCA	70(58.3)	29(76.3)	99(62.9)	
GCA + PMR	50(41.7)	9(23.7)	59(37.3)	0.046
Risk factors				
Hypertension	91(75.8)	30(78.9)	121(76.6)	0.693
Diabetes	20(16.8)	11(28.9)	31(19.7)	0.102
Hyperlipidemia	53(82.8)	11(17.2)	64(40.5)	0.096
Smoker	9(7.5%)	3(7.9)	12(7.6)	1.0
ExSmoker	18(15.0)	8(21.1)	26(16.5)	0.381
Complications				
CHD	25(20.8)	11(28.9)	36(22.8)	0.299
stroke	8(6.7)	11(28.9)	19(12.0)	0.001
Peripheral artery occlusive disease	25(20.8)	4(10.5)	29(18.4)	0.153
Occular Manifestations	24(20.0)	24(63.2)	48(30.4)	<0.001
Ischaemic opticus neuropathy	22(18.3)	24(63.2)	46(29.1)	1
Amaurosis	6(5.0)	3(7.9)	9(5.7)	0.450
Neoplasm post GCA Diagnosis	4(3.3)	11(28.9)	15(9.5)	<0.001
Neoplasm before diagnosis	7(5.9)	5(13.1)	12(7.6)	1
Heart Attack post GCA diagnosis n=75	2(5.3)	4(10.5)	6(7.9)	0.164
Stroke post GCA diagnosis n=75	4(10.5)	7(18.4)	11(14.4)	0.324
Stroke post GCA diagnosis n=75	4(10.5)	7(18.4)	11(14.4)	0.242
Drug Treatments				
Beta-blocker	54(45.0)	15(21.7)	69(43.7)	0.549
ACE inhibitors	39(32.5)	14(36.8)	53(33.5)	0.621
Calcium antagonists	16(13.3)	3(7.9)	19(12.0)	0.568
Insulin	3(2.5)	4(10.5)	7(4.4)	0.058
Metformin	5(4.2)	1(2.6)	6(3.8)	1.0
Statins	44(36.7%)	6(15.8%)	50(31.6)	0.017
Aspirin	68(56.7)	15(39.5)	83(52.5)	0.064
Oral anticoagulation	21(17.5)	5(13.2)	26(16.5)	0.529
Biopsy				
negative	73(60.8)	11(28.9)	84(53.2)	
positive	47(39.2)	27(71.1)	74(46.8)	0.001

Table 4- Mortality outcomes for patient group

Discussion

In this study, we investigated the mortality within a study group of GCA patients seen at the division of Angiology of the department of internal medicine, Medical University of Graz across a 17-year period. Data was also collected for patient characteristics, existing risk factors, complications, drug therapies and biopsy results within this patient group and any association to increased mortality.

As we have not compared our patient group to a control group, the following discussion relates only to results of our GCA group and comparable studies.

Our study revealed five main findings 1) Age at diagnosis is significantly related to subsequent mortality. 2) Patients with a GCA diagnosis alone had higher mortality than those with GCA and additional symptoms of PMR. 3) History of stroke, ocular manifestations and occurrence of neoplasm were significantly related to mortality in GCA patients. 4) Statin treatment had significant effect on survival outcomes. 5) Positive biopsy was further associated with mortality compared to GCA patients with negative biopsy.

Patient Characteristics

Our patient group had a female to male ratio of 2.4:1. Similar studies have found the ratio of females to males to be between (2:1 and 6.3:1) (77,97). General epidemiological studies of GCA populations have found the ratio to be between 2:1 and 7:1 (7,9,12,21).

The study patients exhibited frequent comorbidities of hypertension, diabetes, hyperlipidaemia, and heart disease; this has been found in similar cohort studies. Marie et al 2009 studied 48 patients with GCA, of these 31.3% had arterial hypertension, 4.2% had diabetes, 16.7% smokers, 25% dyslipidaemia, 16.7% ischaemic heart disease (98). Considering the advanced age of the GCA population, this is not an unexpected finding.

The average age of diagnosis in our study group was 71 years which is comparable to other cohorts where age of diagnosis ranges from 70-76 years (93,98-100).

The median age at death in our study was 80.53 years of age, falling in the range of other studies reported age at death; 76.1-85.1 years(92,99).

The mean time to death was 36 months (3 years), other studies had a range of diagnosis to death from 3.71-7.3 years(97,99).

Therefore we feel our patient group is comparable to those of other studies of mortality in GCA patients.

Overall Mortality

The overall mortality of our group was 24.1%, which is comparable to similar cohort studies as shown in Table 5.

Study	Years	n	n Deceased (%)	SMR*	Findings
Current Study	17	158	38 (24.1)	N/A	-
Huston et al 1978	24	41	21(52.2)	-	No effect
Graham et al 1981	10	90	32(64)	-	Increased mortality in women
Begtsson & Malmvall 1981	3-10	90	13(14.4)	-	lower mortality
Andersson et al 1986	17	90	42(44.4)	-	Lower mortality at 5 years, no effect at 10-15 years
Nordorg et al 1989	10	284	82(28.9)	-	No effect
Bisgard et al 1991	13	265	127(47.9)	1.8	Increased mortality
Matteson et al 1996	-	205	49(23.9)	1.034	No effect
Gonzalez-Gay et al 1997	14	109	22(20.2)	0.8	No effect
Gran et al 2001	10	64	13(20.3)	-	No effect
Hachulla et al 2001	18	133	41(30.7)	-	-
Crow et al 2009	14	44	21(47.7)	-	Increased mortality at 5 years
Kermani et al 2014	54	204	154(75.5)	1.0-5.1	Survival reduced in patients with aortic aneurysm / dissection

Table 5- Findings of previous studies on Mortality in GCA patients

*SMR= Standardised Mortality Ratio 1=no difference found between test and control group

Though our study did not look at the mortality compared to a control population, other studies with similar results have done so. However, there are mixed findings in the literature as to the extent that GCA affects mortality. Some studies show no effect on mortality and some show an increase in short and/or long term mortality (5,92,96,99-105). For example, Crow et al found that patients with GCA were more likely to die within the first 5 years following diagnosis than age and gender matched controls, but that survival rates converged at 11.2 years post diagnosis (97). However, Bengtsson et al found mortality to be being lower than in the general population (100) and Jonasson et al. did not see a significant difference in survival compared to the general population (106).

Age at diagnosis was significantly related to mortality, with those patients with an older age at diagnosis more associated to mortality than those with a younger age. Other studies with similar findings have suggested that the older age group may have received higher doses of GCs (101), which may negatively affect the mortality outcomes. However, as we have not compared our results to a control population, we cannot rule out that the higher mortality is not simply due to ageing factors present in the general populace.

Subgroups

Our study findings indicated that a diagnosis of GCA alone was more associated with mortality than GCA with PMR. GCA and PMR are becoming increasingly recognised as different clinical expressions of the same disease. PMR is considered a more systemic expression with primarily musculoskeletal symptoms, whilst GCA patients present with inflammation of the arteries (5). Their differences in pathology may influence the mortality of each group, though the exact reason for this difference has not yet been determined (5). However, one explanation for the better survival of GCA patients with additionally diagnosed PMR might lie in the fact that the systemic manifestations found in PMR are linked to Interleukin-6 (IL-6). Apart from the systemic symptoms, IL-6 has also been found to induce angiogenesis and therefore found to have protective properties against tissue ischemia (33,107), which is a potential explanation for improved survivorship.

A systematic review of PMR and vascular disease found that there is some evidence that PMR is linked to increased risk of vascular disease, but there is

much heterogeneity in the literature, with prospective studies generally showing no association and retrospective studies showing a significant association (108). A 2001 study by Gran et al showed an increase in survival in patients with PMR compared to controls, whilst those with GCA equalled that of the controls. In their case, they hypothesised that the increased survival of PMR patients may be due to increased medical surveillance compared to those with GCA (5). A Swedish study found that vascular mortality was increased in patients with GCA alone compared to those with GCA and PMR (105). However, Bisgard et al found no difference in standardised mortality ratios for subjects that had a diagnosis of arteritis versus those that had PMR (103).

Gender

The current study did not demonstrate any difference of survivorship between males and females. The existing literature has conflicting results on this issue. Decreased survivorship in females has been reported in a few studies (101,105). However, others have reported no gender specific differences (45,106). One study showed decreased survivorship in males (95).

Complications

Of the complications reviewed in our study, patients with history of stroke, ocular manifestations, ischaemic optic neuropathy and those that developed neoplasm post diagnosis were significantly related to mortality.

A history of stroke previous to GCA diagnosis was associated with mortality, but we can not ascertain if this was differing from the general population. Therefore we cannot make inferences attributable to GCA.

In our study patients that developed ocular manifestations or ischemic optic neuropathy were associated with increased mortality. Other studies have also found a relationship between ocular symptoms and decreased survivorship. Hachulla et al found that patients with ocular manifestations had a poorer long-term survival than those without. They hypothesised this may be due to these patients receiving higher doses of GCs, which was also related to mortality (95). Graham et al also found significantly higher mortality in GCA groups with visual manifestations. It was noted that visual manifestations of disease generally occur

in patients over 75 years, which may have accounted for the higher mortality (101).

Patients that developed a neoplasm post diagnosis of GCA had decreased survival compared to those without cancer. There are some studies that have shown an increased risk for developing cancer in GCA and PMR patients compared to the general population (109,110), whilst others have found no significant difference in risk to develop cancer (111-113).

Adjuvant Therapies

Regarding concomitant therapies, the only drug found to have significant effect on mortality in GCA patients were statins. However, as we did not compare to a non GCA control group, the effects on GCA specifically versus general cardio protective effects of statins cannot be ascertained. Narváez et al conducted a comparative analysis by retrospective follow up of 121 GCA patients with and without statin therapy. There was no significant reduction in the incidence of severe ischaemic complications observed in the statin taking group (114). An interesting finding by Lee and colleagues in relation to statins is that within GCA patients, statin and NSAID use lowers the Erythrocyte Sedimentation Rate, which may lead to lower sensitivity and specificity for recognising patients with GCA (115).

Biopsy

Patients with GCA diagnosis confirmed by biopsy had higher mortality than those diagnosed by other criteria or with negative biopsy. A 2001 study by Gonzelez-Gay et al looking at predictive factors for a positive temporal artery biopsy found that there is a subset of GCA patients that are more likely to have a negative temporal artery biopsy. This group also was more likely to have additional diagnosis of PMR, less ischaemic complications, less severe disease, fewer visual complications and lower biological markers of inflammation (116). Additionally the patients had higher haemoglobin levels and a lower ESR rate and platelet count than biopsy positive counterparts (116). These factors may account for the higher mortality association in the biopsy positive group in our study, and may indicate

that patients with positive biopsy may need to be more closely monitored for adverse outcomes.

Aneurysm

No incidence of aortic aneurysm was observed in our study group. However, other cohort studies have found increased incidence of aortic aneurysm in GCA patient. Evans et al studied the frequency of aortic aneurysm and dissection of the aorta in 96 patients. Of these, 11 patients had aortic aneurysm, and compared with matched controls were 17.3 times more likely to develop thoracic aneurysm and 2.4 times more likely to develop isolated abdominal aortic aneurysm (45,90).

However a 2013 study of 6999 patients found only a 2 fold increase of aortic aneurysm, with key risk factors being male gender, age and smoking. The presence of Diabetes was found to be a protective factor.(91)

Neunninghoff et al looked at large artery complications including aortic aneurysm. They found no difference in survival for patients with any kind of large artery complication and those GCA patients without large artery complications. However in patients who developed thoracic aortic dissection, mortality was significantly increased (94). This was also found by Kermani et al, who studied 204 patients with GCA and found that patients with large artery complications had significantly decreased survival compared to those without, and had an standardised mortality ratio of 5.1(93).

Limitations

As a retrospective chart review there are several inherent limitations to our study. There is a lack of uniformity in the detail of medical history in medical records including drug therapies, treatments and outcomes, which may result in missing information. In some cases data was missing regarding cardiovascular outcomes.

The diagnosis to follow up varies between patients, which may affect the reported mortality values.

A significant limitation of the retrospective setting of this study is that we were not able to investigate an age and gender matched control group. Therefore our results are only applicable to our study population and we are not able to comment on whether the numbers and percentages presented are significantly different to those found in the general population.

Given the relationship of GCs treatment to mortality discussed in the introduction to this paper, it would have been useful to collect data pertaining to GC treatments and dosage in this patient group.

Conclusion

In this study we have analysed the outcomes for 158 GCA patients seen at the Graz Angiology clinic between 1995 and December 2012. We were able to demonstrate that several factors are significantly associated with worse mortality outcomes: older age at diagnosis, GCA without manifestation of PMR, presence of ocular manifestations, ischemic optic neuropathy, history of stroke, lack of use of statins and a positive biopsy result. Whilst there were limitations to the study, including inconsistent data and lack of a matched control group, the results are comparable to the literature analysed and represent useful information to inform the clinician on particular patient types that need closer medical monitoring because of the potential higher risk for GCA related complications.

Further research is required to ascertain whether these results are relevant within the GCA group only, and if these results represent significant deviations from the general population in terms of mortality. In addition further research into pathologic pathways, differences between GCA and PMR, that provide explanation to differing mortality rates, is needed.

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