Giant cell arteritis (GCA) is a chronic systemic vasculitis with a marked female predominance and restriction to old age. The disease process distinctly targets large and medium sized arteries, preferentially the aorta and its extracranial branches. Morphological observations indicate that the age and sex distribution of GCA is related to the occurrence of degenerative changes in the arterial wall. GCA is not a truly infectious vasculitis. However, an infection might be a triggering factor. Different centres report an increase in GCA incidence, but annual fluctuations have not been shown to be statistically significant. However, significant seasonal variations have been observed by several groups. The mortality is not increased in adequately treated patients. Although, alternative steroid-sparing agents have been proposed, corticosteroids are still the first treatment choice.

Introduction

Giant cell (temporal) arteritis (GCA) is a chronic, systemic vasculitis, with a distinct tropism for large and medium-sized arteries with well-developed elastic membranes. The inflammatory process preferentially involves the aorta and its extracranial branches, of which the external carotid artery with its superficial temporal division, in particular, is affected. Although major advances have been made in recent years in genetics, molecular biology and the description of the vessel wall morphology, the aetiology and pathogenesis of GCA are still incompletely understood. A single cause or aetiopathological agent has not as yet been identified.

The epidemiology of GCA suggests striking differences in disease risk among ethnic groups, with the highest incidence rates measured in Scandinavia and in subjects of Northern European descent, irrespective of their place of residence [1–5].

Genetic factors appear to be of importance for the development of this disease, with a predominance of certain variants of HLA-DR4 allele expression [6, 7].

Histologically, the inflammatory reaction is granulomatous with highly activated macrophages and T lymphocytes, of which CD4+ T cells are in the majority. Despite its name, giant cells are not a prerequisite for the diagnosis. The local activation of CD4+ T cells in the outer layers (adventitia) of the vessel wall is suggestive of an antigen-driven disease [8]. The possible antigen might be of external origin, but it may also be autologous. The adventitia was proposed to be the centre of the immune response, with the vasa vasorum being the port of entrance of the antigen-presenting cells. The adventitial macrophages and T lymphocytes produce high levels of cytokines, thereby promoting further inflammatory reaction, but not tissue destruction. The macrophages of the media, on the other hand, produce metalloproteinases and oxygen radicals, leading to the disintegration of elastic laminae and further injury of the vessel wall. The tissue cytokine patterns of the temporal artery were correlated with clinical phenotypes of the disease. Thus, high levels of the cytokine interferon-γ (IFN-γ) correlated with cranial symptoms, whereas patients with systemic symptoms only, displayed low levels of this cytokine [9]. Growth factors, such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) are both amply expressed in the inflammatory infiltrate, stimulating intimal hyperplasia. Interestingly, these factors were also produced by the multinucleated giant cells, which are, therefore, not only removers of debris but also secretory.

Thus, the vascular pathology in GCA is the result of immunological injury to the vessel wall, as well as stromal response within the arterial wall [10]. Moreover, significant media atrophy and calcification of the internal elastic membrane (IEM) appear to be prerequisites for its occurrence [11].

The hallmarks of GCA are the systemic inflammation and the inflammatory infiltrate of the vessel wall,
resulting in luminal narrowing and end-organ ischaemia. The most feared acute complications include blindness and infarcts of various vascular territories, whereas the development of mural weakness, resulting in aortic dissection, has been considered a late manifestation [12].

Modern history of giant cell arteritis runs along two paths; that of temporal arteritis (TA) and that of polymyalgia rheumatica (PMR). There is still a controversy over whether PMR and GCA (TA) are linked entities, and specifically if PMR is a vasculitis. Several contributions over the last decade have indicated a similar pathogenetic process in the two conditions. Analyses of the temporal artery biopsies have shown similar patterns of T-cell and macrophage-derived cytokines [interleukin (IL)-1β, IL-6, transforming growth factor-β (TGF-β), IL-2] in biopsy-negative PMR patients as well as in patients with biopsy-proven GCA, but not in age-matched controls. However, IFN-γ was not found in PMR patients, but only in the TA patients, indicating that IFN-γ might be crucial for the development of an overt granulomatous process [9]. These data indicate that PMR patients have a subclinical vasculitis and therefore PMR has been regarded as a ‘forme fruste’ with minor vascular involvement [9]. According to a recent study, using positron emission tomography (PET) with fluoro-18-deoxyglucose (18F-glycose), there was a significantly increased vascular uptake in the large thoracic arteries (aorta, subclavian and carotid arteries) also in PMR patients without clinical or morphological evidence of inflammation in temporal arteries [13]. This investigation gave further support to the contention that PMR and TA are two different expressions of the same underlying disorder and that the large arteries, and not merely the temporal arteries, may be affected in both conditions. Therefore, in this review GCA is used to signify all different clinical manifestations of this disease, also including biopsy-negative PMR.

This review will focus on potential epidemiological clues and issues regarding the aetiopathogenesis of GCA.

Risk factors

Age

GCA is markedly age-restricted. Essentially, no cases younger than 50 yr of age have been identified and the likelihood of being diagnosed with this disease increases continuously with age. GCA is about 20 times more common among people in their 9th decade compared with people aged between 50 and 60 yr [14], which may indicate that its pathogenesis is related to the ageing of the arterial wall [14]. Immunosenescence, the term used for changes in the immune system with ageing, implies a decline in immunocompetence, resulting in an increased risk of infections and autoimmune/inflammatory disorders. Furthermore, a decreased antibody (Ab) production and a shortened duration of protective immunity following immunization are characteristic features in the elderly [15]. Despite much research in this field, basic mechanisms of age-related immune dysfunction have not been clarified. Recently, it was demonstrated that elderly people who failed to produce specific Abs following influenza vaccination showed a predominance of CD8+ CD28− T cells. The aetiology of the CD28− T-cell recruitment is not fully understood in healthy individuals, but there is evidence that these cells might be a response to continued antigenic stimulation. An increased number of autoreactive CD8+ CD28− T cells leads to the production of large amounts of IFN-γ, which might trigger an imbalance in the production of T helper 1 (T_H1) and T_H2 cytokines, and a polarization towards the T_H1 effector type with higher age. Furthermore, in the elderly there is a reduced production of adrenal and gonadal steroids, resulting in less inhibitory effects on pro-inflammatory cytokine production. Changes have also been reported in the activity and reactivity of the hypothalamus–pituitary–adrenal axis [16]. It has been speculated that an imbalance in the production of pro- and anti-inflammatory cytokines could reduce the protection against infections in elderly people and also increase the risk of developing other age-related disorders such as Alzheimer’s disease and atherosclerosis.

Exactly how the ageing of the immune system affects immune reactivity in a patient with GCA has not been investigated.

Gender

There is a clear female predominance in GCA, with 2- to 4-fold more women than men [3–5, 14, 19, 20]. This difference appears to be more marked in the northern parts of Europe. Only in one Spanish study were males reported to be predominant in GCA [21]. Evidence was recently presented indicating that other types of primary vasculitides display an inverse gender preference. An epidemiological review of Wegener’s granulomatosis, Churg–Strauss syndrome and polyarteritis nodosa in the United Kingdom, Spain and Norway showed that, in all areas and in all disease categories, the incidence was higher in men than women, with a peak incidence at the age of 65–74 yr [22]. These vasculitides affect medium-sized and small vessels, in contrast to GCA, which affects large and medium-sized arteries. Consequently, although all these disorders display a peak incidence in elderly people, there appear to be different gender-related factors behind the initial immune stimulation in the two disease groups.

Genetic factors

The possibility of a genetic influence on GCA susceptibility was initially supported by reports of cases among first-degree relatives. Several studies have shown an association of GCA incidence, and risk of visual complications, with the HLA-DRB1*04 alleles [23–25]. However, in isolated PMR, without GCA symptoms, the HLA class II expression varied from one population to another [26]. Genetic polymorphisms with regard to the expression of tumour necrosis factor (TNF), intercellular adhesion molecule (ICAM-1), regulated on activation, normal T-cell expressed and secreted (RANTES) and interleukin receptor antagonist
A recent epidemiological study revealed that the number of pregnancies was lower among GCA patients than among controls. It was suggested that the hyperoestrogenic state during pregnancy protects the artery wall [32]. Oestrogen is involved in a wide variety of different mechanisms which, theoretically, may be related to GCA. It is thus known to preserve a normal vessel wall by stimulating as well as inhibiting the growth of vascular smooth-muscle cells [33–37] and there is evidence that it influences the immune system [38]. One recent study showed that mononuclear and giant cells in GCA display the cytoplasmic accumulation of oestrogen receptor-α (ER-α). Cytoplasmic ER-α was also seen in media smooth muscle in GCA and in non-GCA controls. The nucleotide sequence analysis of the ER-α gene revealed no differences between GCA patients and controls [39, 40]. Whether the reduction in circulating oestrogen in post-menopausal women plays a role in the development of the asymmetrical loss of smooth-muscle cells in the temporal arteries and IEM calcification, which appear to be a prerequisite for the disorder, requires further investigation.

Environmental factors
Since fever, high erythrocyte sedimentation rate (ESR) and general illness are some of its clinical symptoms, GCA has repeatedly been suggested to be infectious. Clustering in disease incidence, as well as rhythmic annual and seasonal fluctuations in incidence, may indicate the involvement of epidemic infections or other exogenous aetiological factors. A study from Olmsted County described a cyclic pattern in the annual incidence during the period 1950–1991, with peaks every 7th yr, each period lasting for about 3 yr [19]. Due to the relatively small number of cases (n = 125), the statistical power was low. The cyclic annual fluctuation was not confirmed in a large series (n = 665) of biopsy-positive GCA in Göteborg in 1976–1995. However, there was a significant seasonal variation with peaks in late winter and autumn [41]. Other studies report peaks in clinical onset during the summer or winter/springtime [42–45]. A Danish study reported a clustering of GCA in relation to two epidemics of Mycoplasma pneumoniae and two major outbreaks of human parvovirus B19 [46, 47]. Interestingly, human parvovirus B19, which infects endothelial cells, has been reported in connection with other vasculitides, such as Wegener’s granulomatosis and cerebral vasculitis in children [48, 49].

Serological studies, including influenza A and B, mumps, adeno-, rota- and enterovirus, Q-fever, leptospirosis, M. pneumoniae and Chlamydia, most of them performed on small series of patients, revealed no difference in seroprevalence between GCA cases and controls [50].

The seroprevalence was also similar in cases and controls regarding viruses known to induce giant cells in humans, i.e. the herpes virus group, Epstein–Barr virus, measles, respiratory syncytial virus and parainfluenza types 1, 2 and 3 [50]. One French study suggested that newly diagnosed cases of GCA were more likely to be positive for IgM anti-human parainfluenza virus type 1, compared with randomly selected sex- and age-matched controls from the general population [51]. Varicella...
Therefore, *C. pneumoniae* infection does not relate statistically to the high prevalence of GCA in Scandinavian women.

To summarize, there is no convincing evidence today that GCA is a truly infectious vasculitis, although it may be speculated that environmental factors such as infections might trigger the immune system in a susceptible host, as suggested by Russo et al. [63], who, in a clinical retrospective study, found a correlation between various infections and the onset of GCA.

**Occurrence**

**Incidence rates**

The incidence of GCA varies greatly in different geographical areas. It has repeatedly been shown that the disease predominately affects subjects of Northern European descent, in particular those of Nordic heritage, irrespective of their place of residence [5–13], with estimates of about 20 cases annually per 100 000 persons older than 50 yr of age. The incidence rates are lower in Southern Europe [64, 65]. Only a few cases are reported in Israel and in black populations [66, 67], while in Asian countries GCA is distinctly infrequent.

The highest figures worldwide were documented from Southern Norway [68] using the 1990 American College of Rheumatology criteria [69]. The annual incidence rate was 32.8/100 000 in individuals older than 50 yr, and 29.1/100 000 for biopsy-proven GCA, thus confirming the high incidence data reported by Gran et al. [5]. Whether such figures reflect a high endemic clustering of GCA in a distinct region or are instead the result of a continuous increase in incidence rates with time is not known.

Clearly, the incidence of GCA has increased in recent years, indicating time trends in morbidity rates. From Göteborg, Sweden, three previous studies from the periods 1973–1975, 1977–1986 and 1976–1995 [3, 14, 41] demonstrated a statistically significant increase with an average annual incidence of biopsy-positive GCA of 16.8, 18.3 and 22.2/100 000, respectively. The relationship between positive and negative biopsies was constant during this period [41]. A similar trend was suggested in Olmsted County, Minnesota [2]. Such observations might reflect genuine changes in morbidity, but they could also be related to greater awareness of the disease or better identification of cases. Other independent causes that might exert an influence are differences in the catchment area of the population studied or an increase in the age of the general population. However, our recent statistical investigation showed that the increase in GCA incidence was not significantly influenced by the increasing age of the Göteborg population (Nordborg et al., in preparation). Furthermore, the study design might differ with a shift from retrospective to prospective studies. The Göteborg studies were all retrospective in design, involving the same catchment area.

As is indicated by the large number of temporal artery biopsies performed, physicians are definitely aware of this disease. On the other hand, taking the data from Östberg [70] into consideration, GCA may be under-diagnosed during life. She found a prevalence of 1.7% in her post-mortem study, including more than 20 000 cases, using the following histological criteria: ‘intimal thickening with narrowing of the arterial lumen, ingrowth of capillaries in media and/or intima, destruction of the elastic membrane with accumulation of mononuclear round cells and/or giant cells’.

Recently, a geographical gradient of frequencies in GCA was reported with a statistically verified increase in frequency by latitude north [22, 71]. The geoepidemiology of other primary systemic vasculitides, such as Wegener’s granulomatosis, Churg–Strauss syndrome, polyarteritis nodosa and microscopic polyangiitis, was recently compared in different European regions [22]; there are differences between geographical areas also in the incidence of small vessel vasculitides. Wegener’s granulomatosis was thus found to be more common in the UK than in Spain, with a trend towards even higher incidence rates in Tromsø (northern Norway), indicating that environmental and genetic factors might also be important in the aetiopathogenesis of these types of vasculitis.

**Mortality**

GCA may be life-threatening. The aorta and its main branches (subclavian and carotid arteries) are the main targets for the arteritic process, but coronary arteries and cerebral arteries are sometimes involved. However, only few fatal cases are reported in the literature. The fact that GCA may cause cerebral and myocardial infarction as well as aortic aneurysms is not general knowledge. Fewer fatal GCA cases are probably detected today, due to decreasing autopsy rates and to the fact that post-mortem histological examination of the arteries is not routinely performed.
Aortic lesions, which are mainly located in the thoracic segment, are asymptomatic in most patients and may therefore be overlooked. Furthermore, their manifestations evolve slowly and an aortic dissection may only be overt years after terminated treatment. In a retrospective study, Evans et al. [12] calculated an increased risk of thoracic aortic aneurysms of 17.3 (95% CI 7.9–33) compared with the general population; the corresponding risk of an abdominal aneurysm was 2.4 (95% CI 0.8–5.5). In Sweden, aortic aneurysms were detected in 6/90 patients after a median follow-up period of 11.3 yr [72]. The prevalence of myocardial infarction in GCA is unknown. The available literature is sparse and limited to case reports. Cerebral infarction has been reported in about 7% of consecutive patients with biopsy-proven GCA [73]. The preventive effect of corticosteroid treatment on mortality has been documented in many long-term follow-up studies [72, 74, 75]. Although one study reported increased mortality early in the disease course, during the first 4 months after the diagnosis of biopsy-proven GCA, the death rates were subsequently normalized [76]. Schaufelberger et al. [77] noticed an increased mortality during the first 2 yr of treatment in patients with biopsy-negative PMR, but not thereafter (personal communication). In the latter two studies the patients were treated by many different physicians without special knowledge of GCA in contrast to the long follow-up study from Göteborg [72], where only doctors with a special interest in the disease were involved.

The risk of fatal complications in GCA stresses the importance of early diagnosis and of follow-up, also after clinical remission.

Occurrence of malignancies in GCA

Malignancy may be associated with polymyalgia rheumatica-like symptoms [78]. However, cancer-related symptoms differ from those of classic PMR; symptoms may appear before the age of 50 yr, they may be asymmetrical and there may be joint pain. Incomplete or delayed relief from corticosteroid treatment is also characteristic. Several papers have addressed the potential association between GCA and the incidence of malignancy. One large study found that malignancies were 2.3 times more common in GCA patients compared with the general population. Considering the long interval between the diagnosis of malignancy and GCA, the relationship appeared weak [79]. So far, there is no proof of a causal association between GCA/PMR and neoplasm.

Treatment

GCA is a highly corticosteroid-responsive disorder. A majority of the patients experience an excellent therapeutic effect. Moreover, this treatment has a preventive effect on vascular complications, as has clearly been shown in many long-term follow-up studies [72, 75].

The time before the initiation of corticosteroid treatment was the single most important factor predicting outcome in patients presenting with symptoms of visual impairment. Among those who were treated within 24 h after loss of sight, an improvement was achieved in more than 50%. In contrast, only 6% of the patients improved when treatment was delayed for more than 24 h [80]. Schmidt et al. [81] emphasized the importance of an early diagnosis and prompt corticosteroid treatment. They reported six cases with severe vascular complications (bilateral blindness, cerebral strokes) on which corticosteroid treatment had no effect. The patient delay between first symptoms (PMR, jaw claudication, headache, amaurosis fugax) and the vascular complication was on average 7 weeks. When a vascular catastrophe is manifest, the corticosteroid therapy, whatever dose chosen, may prevent another vascular incident but does not reverse the symptoms of the first accident.

The optimal initial dose regimen of oral prednisolone, which is the drug most frequently used, has been discussed. According to prospective large series applying acceptable diagnostic criteria, and using predefined treatment protocols, 20–60 mg of prednisolone (mostly 40–60 mg) was shown to be an appropriate starting dosage in about 90% of cases. Alternate-day administration regimens of corticosteroids have not proved effective in GCA [82–84] and this treatment does not reduce the development of steroid-induced osteoporosis [85]. Treatment with intramuscular methylprednisolone was reported to result in a more beneficial side-effect profile in patients with pure PMR in one study [86], although these data were not confirmed in a recent, multicentre, prospective study of biopsy-proven GCA followed up for 1 yr [87]. However, in the latter study, steroids were administered as intravenous pulses, with different kinetics, which might have influenced the result.

Due to the well-known comorbidities related to long-term corticosteroid treatment [88] and the fact that GCA has a remarkably high tendency to relapse during tapering, alternative corticosteroid-sparing therapy has been requested. Several approaches, including combined therapy with cytotoxic (azathioprine, methotrexate and cyclosporin) agents, have been suggested. To date, the vast majority of studies in this field have not led to any firm conclusions, since they are too restricted in number [89, 90], short term [91–93] and biased by high drop-out rates and/or they were uncontrolled [89–91]. So far, methotrexate is the drug that holds the best promise. The results of a randomized, double-blind, 24-month, placebo-controlled trial from Spain, published last year, revealed a significant reduction in the rate of relapses and the cumulative mean dose of corticosteroids was lower in the methotrexate arm compared with the placebo group [94]. Surprisingly, neither the rate nor the severity of adverse events differed between the two groups. The effect on bone mineral density or fracture rate was not evaluated and no information was provided about whether patients with more aggressive disease did better on this treatment. A recent, multicentre, placebo-controlled trial [95] showed no benefit of methotrexate treatment in terms of the number of relapses, treatment failures, cumulative steroid doses or treatment toxicities. However,
the number of patients included was small, which reduced the power of this study.

New drugs such as TNF blockers have rapidly emerged as efficient treatments in rheumatoid arthritis [96]. Regarding their use in GCA, the experience is limited to case reports, albeit with some encouraging results. Cantini et al. [97] reported a complete response in three of four patients with long-standing active giant cell arteritis, still requiring high doses of prednisolone after more than 42 months. All patients had developed serious corticosteroid-related side-effects. After two infusions with infliximab (3 mg/kg), three of the patients displayed a clinical and humoral remission. The remission sustained after a third infusion and during a follow-up time of 6 months, despite withdrawal of the corticosteroids. One patient, who did not respond to therapy, was withdrawn after the second infusion, in accordance with the protocol. The therapy was well tolerated by all patients. No side-effects were reported.

Interestingly, the same group recently reported a similar good response with normalization of clinical and serological activity after three infusions with infliximab in three of four patients with persistent PMR, without cranial symptoms [98], whereas one patient had a partial effect. In the good responders corticosteroid therapy was terminated and in the partial responder it was reduced by 50%. The remission was sustained at the control 1 yr after the first infusion. Infliximab was well tolerated; there were no side-effects. These open pilot studies suggest that TNF-α blockade may have a steroid-sparing effect in patients with corticosteroid-resistant GCA.

In a critical review of treatment studies, it was suggested that only about 10–15% of patients have a ‘corticosteroid-resistant’ disease, defined as a daily requirement of >15–20 mg of prednisolone more than 2 months after the start of therapy [99]. These patients require a safe and effective additional agent. Future trials should focus on appropriately defined large cohorts of patients, ideally biopsy-proven patients, who need >15 mg of prednisolone as chronic maintenance treatment. The rate of remission in the long run is another important issue which must be focused on increasingly in new treatment modalities.

The characteristic prompt relief of symptoms and preventive effect on vascular complications after the initiation of corticosteroid therapy in the vast majority of patients indicates the unique role of steroid-mediated immunosuppression in GCA. Corticosteroids have been regarded as the cornerstone in the therapy of GCA and today there is little evidence, if any, that they can or should be replaced. On the other hand, despite good clinical improvement in the systemic signs of the disease, the inflammatory infiltrate persists for a long time in the vessel wall, which further emphasizes the need for optimized therapy in GCA.

Recently, the biological action of corticosteroids was elucidated, using temporal arteries with biopsy-proven GCA explanted into immunodeficient SCID mice [100]. NFκB-dependent cytokines (IL-2, IL-1β, IL-6) were suppressed, whereas TGF-β and IFN-γ did not appear to be influenced, despite high doses of corticosteroid treatment. These observations provide an explanation for the promptness of the therapeutic effect seen in glucocorticosteroid treatment, but they also indicate why patients have to be treated for a long time. Persistent disease is evidenced by active histological lesions, as well as by the fact that patients develop aortic aneurysms even years after they were considered to be in remission [12].

**Osteoporosis**

The age of the GCA population puts them at great risk for corticosteroid side-effects, of which osteoporosis leads to the most severe sequelae. In contrast to increased resorption, resulting from the disease process, the steroid-induced loss of bone is due to decreased formation of bone. However, studies of corticosteroid-related osteoporosis morbidity in GCA have produced contradictory results. Pearce et al. [101] reported that even small daily doses of 6 mg of prednisolone might result in bone loss, initially in trabecular bone, such as the spine, followed by cortical bone. On the other hand, in a recent Norwegian study the authors focused on bone mineral density of the radius, spine and hip, measured by dual-energy X-ray absorptiometry (DEXA) in GCA (PMR and TA). Patients currently or previously treated with prednisolone were compared with 30 newly diagnosed cases of GCA (PMR or TA), examined prior to the start of corticosteroid therapy, and with 70 healthy controls. For current users the mean daily dose was 6.5 mg of prednisolone, the mean cumulative dose 7.7 g, and for previous users 5.6 mg and 6.6 g, respectively. No statistically significant difference was found between any of the four groups [102]. A British prospective study over 2 yr in patients with PMR [103] showed increased levels of cross-links (resorption markers) before the start of corticosteroids, and a significant decrease at 6 months. Bone mineral density (BMD) at 1 yr correlated with ESR at baseline, but not with the cumulative dose of corticosteroids. The last study stresses the impact of the systemic inflammation per se on bone mass. Thus, the morbidity of bone loss in GCA is multifactorial. If BMD is within the normal range, the bone-sparing agents calcium and vitamin D should be given generously to patients at the start of treatment with corticosteroids. Bisphosphonates could be instituted if BMD shows decreased bone density on the DEXA scan. In patients for whom corticosteroids are an unavoidable necessity, always try to use the lowest possible dose to suppress the inflammation, at initiation and during maintenance therapy.

**Conclusions**

GCA is suggested to be an antigen-driven disease, where the antigen might be exogenous or endogenous. A single cause or aetiologic antigen has not as yet been found. There is no proof that GCA is a truly infectious disease and, on morphological and epidemiological grounds, there is no reason to believe that atherosclerosis initiates or is a risk factor for GCA. For the future, efforts should...
be made to identify further relevant environmental, age-related, genetic and, in particular, gender-specific risk factors.

Corticosteroids remain the cornerstone of drug treatment of GCA. Future large trials, divided into clinically important subgroups, may provide information about the optimal therapy for each patient with GCA. Other approaches with new drugs, such as TNF-α blockades, might hold promise but have not as yet been tested in controlled trials in GCA.

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