The value of duplex in systemic giant cell vasculitis

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This research aims the usefullness of duplex mapping in systemic giant cell vasculitis. In determing the diagnosis, the duplex will be compared with the current gold standard, the 18F-FDG PET-CT, looking at the sensitivity and specificity of the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Observational non invasive

Summary

ID

NL-OMON39324

Source
ToetsingOnline

Brief title
The value of duplex in systemic giant cell vasculitis

Condition

- Autoimmune disorders
- Vascular disorders NEC

Synonym
giant cell vasculitis, vesselinflammation

Research involving
Human

Sponsors and support

Primary sponsor: Sint Elisabeth Ziekenhuis
Source(s) of monetary or material Support: Geen extra geldstroom.

Intervention

Keyword: duplex, follow-up, Giant cell vasculitis, serummarkers

Outcome measures

Primary outcome

The suspicion of a systemic reuscelvasculitis is based on issues such as elevated inflammatory parameters, reasonably excluding of infections, malignancy and other systemic diseases, complaints of malaise and / or fever or presence of claudication and / or ischemia. Diagnosis is made based on the gold standard nowadays: 18F-FDG PET-CT.

Endpoints will include:

1. Sensitivity / Specificity of the duplex (vs. Gold standard: PET)

a. In addition specifying this by specific arteries

2. Value of duplex during follow-up

a Increase edema = exacerbation vasculitis?

b. Decreased edema = vasculitis recovering? (and affected therapy?)

Secondary outcome

1. If the duplex shows evidence of giant cell vasculitis (halos), we will try to show at fixed intervals after initiation of treatment, how long there remain visible halos and how they change. This will be done after 4 and 8 weeks and every 8 weeks untill disappearens. Also, the duplex will be repeated when a exacerbation of the vasculitis is suspected. 2. How systemic is the vasculitis?

Study description

Background summary

Giant cell vasculitis is a (medium) large vessels vasculitis. Most famous within the giant cell vasculitis is the subgroup temporal arteritis. This disorder was first described in 1890 by Hutchinson. The exact etiology of giant cell vasculitis is unknown. Several hypotheses have been postulated, including infectious (parvovirus B19), genetic (HLA-DRB1 and HLA-DR4), and auto-immuun. The pathogenesis is a T-cell mediated vasculitis which is activated by the in the adventitia located dendritic cells. On microscopic examination this is seen as a transmural and segmental granulomatous (mononuclear) inflammatory infiltrate consisting of such CD4 + T cells and giant cells. These giant cells are not obligatory and are only found in about 50% of the patients.This leads to intimahyperplasia, which ultimately can lead to stenosis and occludering with ischemia. Last years there is a growing attention for the more systemic 'entity' , a form which is still unknown. It is unclear what the exact relationship to the (typical) temporal artertitis is. Maybe in a few years will be proven that the two separate entities are all one systemic disease. There is growing evidence for the this. For more than 50% - 75% of the newly diagnosed temporal arteritis there is any involvement of the great arteries and thus a systemic reuscelvasculitis. In about 15% of the cases at diagnosis of a temporal arteritis there is even a dilatation of the aorta. Besides the involvement of vessels frequently described (as the aorta and extracranial branches), almost all arteries can participate. But also conversely the temporal artery can (asymptomatic) participate in systemic giant cell vasculitis. How often the temporal artery is also involved and how often it is possible with suspected systemic illness to use the temporal artery for diagnostic use is unknown. Many other manifestations of giant cell vasculitis have been described, from a mega-aortic syndrome to affected relatively small arteries such as in the ovaries and cervix. But also hepatogenic involvement to affected limbs or mammae. The incidence and prevalence of systemic giant cell vasculitis is difficult to determine, particularly given that in the literature, different names are used (arteritis and vasculitis, systemic and extra-cranial), and therefore no distinction is made in how systemically the disease is. Often prevalences expressed by the affected artery instead of each individual. In addition, the disease may still be insufficiently recognized (such as primary causes of aneurysms) or there are subclinical forms which we at the moment even do not recognize yet. Given that systemic giant cell vasculitis can be manifest on very many different locations, it also means that the presentation of the disease is very atypical and varied. It is therefore really the clinician whether and when there will be thought of a systemic giant cell vasculation. In particular, also because there are no diagnostic criteria for this entity. Many described symptoms including fatigue, (sub) febrile temperature, weight loss, malaise and an elevated ESR. Less commonly, patients

present themselves with symptoms of claudication or ischemia. Given the fact that there is no single presentation it will be interesting to (retrospective) see the original presentation in this research. When in this patient population then, after a reasonably exclution of infection, malignancy or other systemic disease, a PET-CT is performed, there often seems to exist a giant cell vasculitis. Sometimes only in a very late stage, while literature demonstrated that the provision of early diagnosis of giant cell artiritis can influence the prognosis. Most of the complications described in (late diagnosed) giant cell vasculitis is blindness because of anterior ischemic optic neuropathy (AION) (15-30%), transient ischemic attacks and stroke (3-4%), aneurysm formation and dissection of the thoracic aorta (<15%). To influence the diagnostic process and any late diagnosis, we need alternative accessible diagnostics which are also less invasive and burdens

ome for a patient. For the diagnosis of systemic giant cell vasculitis are no existing diagnostic criteria. Today, the gold standard is still the 18F-FDG PET-CT, regardless of what symptoms or abnormalities patient presents with. Several studies show that a PET-CT appears useful as a diagnosticum a for giant cell vasculitis but much less good at follow-up or relapse. Given that diagnosis is based entirely on imaging, standardized guidelines or diagnostic criteria seem essential for this. Even though several attempts have been made to check out by means of scoring systems or comparisons of intensity with the liver, there is still a need for a universal method. Besides the fact that there is no uniformity in the diagnosis using PET, ther are other problems as that sensitivity of PET scan for Giant Cell-arteritis depends on the degree of inflammation, it's not possibel to check the PET involvement of the temporal arteries due to the small diameter and its location next to the brains and finally, the PET-CT is also another invasive, burdensome, not (very) accessible and pretty expensive. Reason enough to investigate en develop alternative more standardized research methods like an echo duplex, of which already good results have been described, among other things, with 100% detection of

affected arteries in upper and / or lower extremities at this patientgroup. There is increasing awareness about the additional value of duplex examination of the temporal artery in the diagnosis of temporal arteritis. Duplex examination can show halos, increase flow and stenoses and occlusions. In this the halo is particularly important given that stenoses and occlusions of the temporal artery are frequently seen in the elderly population, such as a sign of atherosclerosis. Stenoses and occlusions of the temporal artery are therefore not specific to the disease. These halos have a sensitivity ranging from 40-86% and a specificity ranging from 78-100% in temporal arteritis, this is a positive predictive value of 75-92% and a negative predictive value of 64-96%. About the applicability of a duplex in systemic giant cell vasculitis is still very little known. As a relatively few invasive, accessible and inexpensive available diagnostic tool, we want to try using this research to gain more insight into the position of the duplex in the diagnosis, treatment and follow-up of systemic giant cell vasculitis. It will also try to understand which vessels most often affected and thus usefulness in the clinic. Partly based on the fact that in 29% of patients with temporal arteritis duplex examination also shows deviations from the larger vessels, including carotid artery, subclavian artery and femoral artery, particularly vascular edema / halos, indicating systemic vasculitis.View the fact that it is known that an false-positive duplex can be seen in infection, malignancy, vasculitis, and otherwise absent flow in the adjacent vein, it is important to use a control group so clear conclusions can be drawn. In the follow-up phase, we try to make use of the fact that there is an evolution in the degree of edema. Where we must observe that a duplex may be false-negative in the early (with no vascular edema) and in the late phase of inflammation (decrease edema vessel). The literature has shown that duplex abnormalities are seen about 16 (7-56) days after starting treatment with corticosteroids. We want to see if this applies to all patients treated in our population and see what the average duration of these duplexabnormalities is. We would also like to see what happens to the duplex abnormalities during treatment or recurrent symptoms and if a decrease or increase in bloodmarkers is correlated to the decrease or increase of the vesseloedema. In addition to the PET-CT, the additional diagnosis tests of laboratory tests, in which an increased ESR and CRP are most often used. The ESR has a sensitivity of 76-82%, but only a specificity of 9%. 60% of patients have a ESR> 100 mm / h, 89% ESR> 50mm/uur, 95% a ESR> 40 mm / hour. The CRP has a sensitivity up to 97.5%.

Also, anemia, thrombocytopenia and elevation of liver enzymes are seen (20-30%) .Despite the relatively high sensitivity, better serum markers are highly desirable, both as a diagnostic (hopefully with better specificity) and at follow-up. From the pathophysiology of giant cell vasculitis it is now known that the activation of dendritic cells release inflammatory cytokines such as IL6 and IL8, which then stimulates the activation of the T cells and inflammation again. In addition, macrophages also release cytokines IL1 and IL6, which contribute to the systemic features of temporal arteritis. Precisely these cytokines seem to play an important role in the pathogenesis of giant cell vasculitis. Something recent therapeutic studies, with the so-called IL6 inhibitors, already seem to support. In addition to IL-6, there is also evidence that other serum markers may be useful in giant cell arteritis. One of the larger studies on this part shows that a significant elevation of titer of ESR, CRP, intercellular adhesion molecule (ICAM) -1 and PDGF between patients with relapse and other control patients without relapse. When looking within 1 patient between the time of relapse and stable disease, the following markers are rise significant: BSE (77 vs 20 mm / h), CRP (1.90 vs 0.5 mg / dl), ICAM-1 (298.33 vs. 235.70 ng / ml), TNF-a (10.95 vs 2.45 pg / ml) and IL-12p40 (60.06 vs 7.80 pg / ml). This study was unable to demonstrate significant increase of IL-6, as opposed to in another study, in which IL-6, was possibly even more sensitive than ESR. Finally, there are indications that anti-cardiolipin antibodies may be a good marker. All in all, untill now there is no consensus on any new (and better) markers and enough research in this area is desired. Reason enough involve these new serum markers in this study.

Study objective

This research aims the usefullness of duplex mapping in systemic giant cell vasculitis. In determing the diagnosis, the duplex will be compared with the current gold standard, the 18F-FDG PET-CT, looking at the sensitivity and specificity of the duplex compared to the control group without systemic giant cell vasculitis. Efforts will be made to further specify the subgroups of vessels where this is going to be possible. Furthermore, the value of duplex during follow-up period will be examined as well. Particular we will try to evaluate the usefullness of decrease / increase of edema and to assess if this corresponds respectively to a restoring or a exacerbation of the vasculitis, where an increase in ESR has to be the control, as we use this at the moment. It is interesting therefore to infer whether it should be possible to adapt this treatment sooner and perhaps to reduce with prednisolone. Finally, we will evaluate how systemic reuscelvasculitiden most often are and will check for new serum markers.

Primary Objective:
• Sensitivity and specificity of the duplex examination at systemic giant cell vasculitis as compared to the current gold standard (18F-FDG PET-CT)
• Value of duplex during follow-up
o Increase edema = exacerbation vasculitis?

o Decrease edema = healing vasculitis? (And affected therapy?)

Secondary Objective (s):
• Specifying sensitivity and specificity of duplex to affected vessels
• How systemic is the vasculitis?
• Role of new serum markers in the diagnosis of systemic giant cell vasculitis and the temporal arteritis.
• Duration that duplex abnormalities persist after initiation of therapy with corticosteroids
• Retrospective initial presentation of systemic giant cell vasculitis

Study design

In this prospective, cohort study, all patients with 18F-FDG PET-CT proved giant cell vasculitis wil be investigated. Only patients seen within the St. Elisabeth Hospital or the TweeSteden Hospital in Tilburg by a neurologist, internist, rheumatologist or ophthalmologist are included.

Flowchart:
1. All patients with 18F-FDG PET-CT proved giant cell vasculitis, seen by a neurologist, internist, rheumatologist or ophthalmologist.
*
2. Duplex examination and blood tests according to protocol
*
3. Treatment and follow-up according to the guidelines
*
4. When the first duplex was abnormal with the presence of halos, a control duplex wil be performed 4 weeks and 8 weeks (and every 8 weeks later with still persisting abnormalities) after initiation of therapy with corticosteroids. If an exacerbation of the vasculitisis suspected (increased symptoms or increased blood disorders), a control duplex is performed as well.
*
5. Outpatient control after last duplex, further follow up according to the guidelines
*
6. Analysis results in termination research

Study burden and risks

The burden exist of extra duplex investigations and once an extra tube of blood during.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

PET-CT proven giant cell vasculitis

Exclusion criteria

Legally incapable patients

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-10-2012
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	03-07-2012
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-04-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL40657.008.12