Project Description

Evaluation of the ultrasounds role in patients suspected to have cranial and extracranial giant cell arteritis.
(**E**valuering af **U**ltralyds **R**olle hos patienter med mistanke om **E**kstrakranial og **K**ranial kæmpecelle **A**rteritis (**E.U.R.E.K.A**))

1. Background

Giant Cell Arteritis (GCA) is the most common systemic vasculitis and the incidence is higher in Scandinavian populations, even after migration to other parts of the world (1). GCA specifically involves large arteries particularly the branches from the aorta towards the head and neck. There is no true gold standard for the diagnosis of the condition, and the closest to this is a positive temporal artery biopsy (TAB). Despite a high clinical suspicion of GCA, a biopsy result can be "false negative". There is a low sensitivity when comparing the biopsy and the clinical diagnosis (2, 3), with up to 44% of the biopsy-negative patients clinically diagnosed as having GCA (4,5). There are various reasons for TAB can be negative. Skip lesions have been reported in 8.5 and 28% of TABs from patients with GCA in two previous studies (6, 7), and it is likely that such discontinuous inflammatory changes in the temporal artery may cause false-negative biopsy results. In addition, GCA alone can be localized in the extracranial arteries, and not in the TA (8).

The American College of Rheumatology (ACR) have developed classification criteria for GCA but these are primarily designed to distinguish one form of vasculitis from another form of vasculitis rather than distinguish patients who have headache of a non-specific nature from those who specifically have GCA (9). ACR classification criteria emphasize the affection of the temporal artery (TA); nonetheless, there are GCA patients with primary affection of carotid (AC), axillary (AA) and/or subclavian artery (8, 10, 11).

Early diagnosis and treatment of patients with GCA are important because patients may develop significant complications including blindness and stroke. Irreversible visual loss occurs in up to 20% of patients (12, 13, 14) There are few predictors of cranial ischemic events and jaw claudication is one of these (12,14) . Facial artery partly supplies the jaw region (16). The incidence of facial artery (AF) involvement in GCA patients and its correlation to ischemic symptoms has not been investigated before.

The GCA patient population has an older age and many co-morbidities that makes very important the factor of avoiding not necessary high dose of corticosteroids (CS) (15). In patients with high

GCA suspicion the physicians initiate CS treatment without waiting for the histopathological results. In Denmark, it is estimated that the time between the initiation of CS treatment and TAB histopathological results is around 10 days.

Relapses rates under CS tapering are high (40-50%) (17) and relapse rates are commonly used primary endpoint in clinical trials with patients with GCA; however, limited data exists regarding the clinical characteristics and predictors of relapses (18).

US is increasingly used for the diagnosis of GCA. Schmidt et al. (19) described for first time in 1995 the 'halo sign ", a hypoechoic circumferential thickening of arterial intima-media complex (IMC), which is probably due to oedema of the vessel wall (indication of inflammation).

Another way to demonstrate the inflammation in TA the so called "compression sign" could be also used; the artery wall cannot be completely compressed after increased press is applied with the transducer due to inflammation and subsequent thickening of IMC (20).

The newer US transducers with high frequency have a resolution of 0.1 mm, that allows the clear visualisation of the halo sign, in addition to monitor the vascular changes after the initiation of CS (21, 22). There is scarce information about the time required for halo disappearance after the introduction of CS, and no data exist regarding the correlation between disease relapse and persisting IMC thickening in both cranial and extra-cranial arteries (22).

Vascular US for GCA diagnostics is highly operator dependent and it is important to develop expertise with the technique before applying it, therefore adequate training is essential. In an effort to standardize the technique and provide adequate training the 1st International Workshop on Ultrasound in Large Vessel Vasculitis & Polymyalgia Rheumatica was held in 2013 scientifically endorsed from the European Leaguer Against Rheumatism (EULAR) (23).

There are not any multicentre ultrasound studies, assessing the value of ultrasound examination of cranial and extracranial arteries as an adjunct to diagnosis of GCA.

2. Research Objectives

- **Main objective**

To explore the diagnostic accuracy of US examination of the cranial (TA and AF) and extracranial vessels (AC, AA) compared to biopsy in patients suspected to have GCA in a Danish setting/population.

- **Secondary objectives**

1. To investigate whether US guided TAB can increase the amount of positive TAB results.

2. To investigate whether GCA patients with AF affection have higher rates of ischemic symptoms compared to those without.
3. To investigate whether vasculitis of the cranial and extracranial vessels can be detected by US six months after the initiation of CS treatment and if it is correlated to higher relapse rates.
4. To investigate the inter-observer agreement in the assessment of images/films of vascular scanning in patients suspected for GCA.

3. Study procedures and subject enrolment

This is a multicentre, prospective, non-interventional observational study. Patients suspected to have GCA will be included with a follow-up visit after 6 months for confirmation of the diagnosis.

- **Clinical data collection method**

i. ***Baseline visit:***

At the inclusion a careful history and clinical examination of patients will be performed. Patients will be treated and followed according to standard clinical practice, such as listed by the Danish Society of Rheumatology Clinical Guidelines (24).

Patients will be evaluated in relation to the ACR classification criteria for GCA (1) (Table 2). US operator has no involvement in the inclusion and initial treatment decision.

At baseline, a plethora of clinical data will be collected (Table 2). Cranial ischemic symptoms are defined as: jaw/tongue claudication, stroke, transitory ischemic attack, Anterior Ischemic Optic Neuropathy (AION), amaurosis fugax, diplopia, permanent visual loss.

ii. ***Six months visit:***

At 6 months the verification of diagnosis (expert opinion) will be done by a rheumatologist blinded to all US results. There will be retrospectively collected clinical data from patients journal investigated the eventually incidence of GCA relapses in every patient (table 3).The clinician that collected the data is blinded to initial and 6 months US examination results.

- **Relapse or recurrence is indistinctly defined as reappearance of disease-related symptoms categorized into four groups:**

i. PMR symptoms (stiffness, pain in shoulder and /or hip region),
ii. Cranial symptoms (headache, scalp tenderness, jaw claudication, visual manifestations),
iii. Systemic disease (fever, weight loss and increased inflammation markers without any other explanation),
iv. Symptomatic large vessel involvement (extremity claudication).

- **Temporal artery biopsy:**

All patients suspected for GCA underwent a TAB that is a standard examination. TAB performed as soon as possible after the end of the US examination. TAB will be evaluated by the local pathologists. In Esbjerg and Silkeborg hospital all EUREKA patients will be randomized 1:1 to either US guided or blind TAB (Table 2) - the later is common standard practice. The TAB will be performed by experiences surgeons (Dr. Knud Larsen in SVS Esbjerg and Dr. Per Søndergaard in Regional Hospital Silkeborg). In Glostrup hospital all TAB will be taken blind by a random surgeon (there was not possible to make an appointment with the relevant surgical department).

- **Ultrasound Diagnostic Studies:**

At inclusion to the study and 6 months later will be performed a vascular scanning of 12 vessels: Bilateral evaluation of 3 branches of TA (common, parietal and frontal), AF, AC and AA.

All US examinations will be conducted with the same equipment in each centre (Hitachi Preirus/Ascendus in Esbjerg / Silkeborg, GE Logic 9E in Glostrup) and apply equal settings (table 1). Equipment settings, scanning techniques and image analysis will be performed according to the International Workshop on Ultrasound in Large Vessel Vasculitis & Polymyalgia Rheumatica standards.

All arteries are examined in longitudinal as well as transversal view. In both projections, both B-mode and colour Doppler examination will be performed. The IMC of AC and AA will be measured and colour Doppler video clip of 2-3 sec will be stored in an image database. The images will be evaluated (table 4) by a rheumatologist with long experience in GCA ultrasound (11) (Andreas Diamantopoulos-AD) who makes the final US diagnosis. AD is blinded to all clinical, laboratory and biopsy data.

- **Definition of ultrasonographic vasculitis**

A positive sign for vasculitis in TA braches and in AF is defined as a hypoechoic IMC thickening (halo sign) and or a positive compression sign. AT, AF have widely variable diameter, therefore, is a specific IMC thickness as the cut-off for vasculitis is not defined. A homogeneous IMC increased thickness in AA of IMC ≥1mm and IMC ≥1,5mm in AC will be will be defined as vasculitis(11).

Ultrasonographic training

Five rheumatologist from Denmark with many years of experience in the use of musculoskeletal ultrasound (Doppler inclusive), have been trained at the "International Workshop on Ultrasound in Large Vessel Vasculitis & Polymyalgia Rheumatica" (3 days training included 5timers theory and 10 hours of hands-on). In addition, all ultrasonographers participated in a 2 days' workshop with US examination of 4 healthy persons and 4 GCA patients, organized by the investigators on the

Department of Rheumatology in Esbjerg under the supervision of AD (total 6 hours of supervised hands-on and one hour image evaluation).

- **Interobserver agreement**

US images/videos will be evaluated by the performing ultrasonographer before the TAB assessment and then the pictures will be evaluated by the blinded US expert. Table 4 will be used for vessel evaluation. An interobserver agreement analysis will be performed, regarding the patient diagnosis (0=Healthy, 1=Sick) and the vascular affection (0=Normal Vessel, 1=Affected vessel). For the evaluation of the interobserver agreement in AT the golden standard will be the TAB results; while in the rest of the vessels the golden-standard will be the US expert assessment.

4. Subject selection

- Inclusion criteria

i. Age> 50years

ii. Signs and symptoms which indicates the presence of GCA: new localized headache, jaw claudication, tenderness of AT, reduced pulsation in AT, scalp tenderness, new-onset visual disturbances (AION, amaurosis fugax / diplopia), elevated inflammatory parameters without other explanation(CRP and/or ESR), polymyalgic symptoms.

iii. The patient must be able to consent.

- Exclusion criteria

i. Previous GCA diagnosis

ii. Use of> 20 mg corticosteroids for more than 7 days before the ultrasound examination and tissue sampling.

iii. Long-term use (> 1 month) of <20 mg prednisolone daily until 3 months before study start.

iv. Mental disease and/or misuse of alcohol or drugs that affects patients' ability to give informed consent.

v. Unable to have an US examination and/or TAB within 7 days after initiation of corticosteroids.

5. Biostatistical analysis

The statistical calculations carried out in collaboration with the bio-statistician Rene Holst from the University of Southern Denmark who will provide statistical support to this project.

The power calculation was based on a specification with a sensitivity and specificity of 90% for the US diagnostic and using a significance level of 5% and power of 80%. There is expected that approximately 60% of the included patients will have a positive temporalis artery biopsy. This indicated a need for 100 patients. http://www.statstodo.com/SSizSenSpc_Pgm.php".

Sensitivity and specificity will be estimated during the analysis and using the outcome from the expert opinion as the "true" diagnostic state. The causes for potential deviations between the three diagnostics (US vs Expert opinion vs. ACR criteria) will be analysed for by a logistic regression with the outcome from the US and ACR criteria as the response variable (0=healthy 1=Sick) and using the expert opinion outcome in combination with other variables of interest (gender, age) as predictors.

Interobserver agreement will be calculated with the help of Cohen kappa coefficient. Also an intra Class Correlation (ICC) will be estimated by use of a mixed effects model, where the analysis will adjust for gender, age and other covariates of interest. The ICC will reflect how much of the total random variation that can be attributed to disagreement between the observers.

- **Publication plan**

i. The diagnostic accuracy of ultrasound as an alternative to temporal artery biopsy for the diagnosis of GCA in patients suspected to have GCA.
ii. The diagnostic value of US guided TAB. A randomised control study.
iii. The incidence of fascial artery involvement in GCA and its correlation to cranial ischemic symptoms.
iv. Six months US evaluation of the cranial and extracranial vessels and US utility as a relapse predictor.
v. Evaluation of inter-observer agreement in the assessment of cranial and extracranial vascular US scanning in patients suspected for GCA.

6. Ethics committee approval

The study is approved by the regional committee on medical health ethics (Project-ID: S-2014003) and the Danish data protection agency.

7. References

1. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, Miranda-Filloy JA,Gonzalez-Juanatey C, Martin J, Llorca J. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum. 2009 Oct 15;61(10):1454-61. doi:10.1002/art.24459.

2. Lenton J, Donnelly R, Nash JR. Does temporal artery biopsy influence the management of temporal arteritis? QJM. 2006 Jan;99(1):33-6. Epub 2005 Nov 15.

3. Davies C, Frost B, Eshan O, McLain AD, Shandall A. Temporal artery

biopsy...who needs one? Postgrad Med J. 2006 Jul;82(969):476-8.

4. Hall S, Persellin S, Lie JT, O'Brien PC, Kurland LT, Hunder GG. The therapeutic impact of temporal artery biopsy. Lancet. 1983 Nov 26;2(8361):1217-20.

5. Schmidt WA, Gromnica-Ihle E. Incidence of temporal arteritis in patients with polymyalgia rheumatica: a prospective study using colour Doppler ultrasonography of the temporal arteries. Rheumatology (Oxford). 2002 Jan;41(1):46-52.

6. Poller DN, van Wyk Q, Jeffrey MJ. The importance of skip lesions in temporal arteritis. J Clin Pathol. 2000 Feb;53(2):137-9. PubMed PMID: 10767830;

7. Campbell RJ, Hunder GG, Carney JA. Skip lesions in temporal arteritis. Mayo Clin Proc. 1976 Aug;51(8):504-10.

8. Schmidt WA, Seifert A, Gromnica-Ihle E, Krause A, Natusch A. Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. Rheumatology (Oxford). 2008 Jan;47(1):96-101.

9. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990 Aug;33(8):1122-8.

10 . Schmidt WA, Natusch A, Möller DE, Vorpahl K, Gromnica-Ihle E. Involvement of peripheral arteries in giant cell arteritis: a color Doppler sonography study.Clin Exp Rheumatol. 2002 May-Jun;20(3):309-18.

11. Diamantopoulos AP, Haugeberg G, Hetland H, Soldal DM, Bie R, Myklebust G. Diagnostic value of color Doppler ultrasonography of temporal arteries and large vessels in giant cell arteritis: a consecutive case series. Arthritis Care Res(Hoboken). 2014 Jan;66(1):113-9. doi: 10.1002/acr.22178.

12. Liozon E, Herrmann F, Ly K, Robert PY, Loustaud V, Soria P, Vidal E. Risk factors for visual loss in giant cell (temporal) arteritis: a prospective study of 174 patients. Am J Med. 2001 Aug 15;111(3):211-7.

13. Nesher G, Berkun Y, Mates M, Baras M, Nesher R, Rubinow A, Sonnenblick M. Risk factors for cranial ischemic complications in giant cell arteritis. Medicine(Baltimore). 2004 Mar;83(2):114 22.

14. González-Gay MA, Blanco R, Rodríguez-Valverde V, Martínez-Taboada VM, Delgado-Rodriguez M, Figueroa M, Uriarte E. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. Arthritis Rheum. 1998 Aug;41(8):1497-504.

15. Harris E, Tiganescu A, Tubeuf S, Mackie SL. The prediction and monitoring of toxicity associated with long-term systemic glucocorticoid therapy. Curr Rheumatol Rep. 2015 Jun;17(6):513. doi: 10.1007/s11926-015-0513-4.

16. Yang HJ, Gil YC, Lee HY. Topographical anatomy of the transverse facial artery. Clin Anat. 2010 Mar;23(2):168-78. doi: 10.1002/ca.20880.

17. Martinez-Lado L, Calviño-Diaz C, Piñeiro A, Dierssen T, Vazquez-Rodriguez TR, Miranda-Filloy JA, et al. Relapses and recurrences in giant cell arteritis: a population-based study of patients with biopsy-proven disease from northwestern Spain. Medicine (Baltimore) 2011;90:186–93.

18. Alba MA, García-Martínez A, Prieto-González S, Tavera-Bahillo I, Corbera-Bellalta M, Planas-Rigol E, Espígol-Frigolé G, Butjosa M, Hernández-Rodríguez J, Cid MC. Relapses in patients with giant cell arteritis: prevalence, characteristics, and associated clinical findings in a longitudinallyfollowed cohort of 106 patients. Medicine (Baltimore). 2014 Jul;93(5):194-201.doi: 10.1097/MD.

19. Schmidt WA, Kraft HE, Völker L, Vorpahl K, Gromnica-Ihle EJ. Colour Doppler sonography to diagnose temporal arteritis. Lancet. 1995 Apr 1;345(8953):866.

20. Aschwanden M, Daikeler T, Kesten F, Baldi T, Benz D, Tyndall A, Imfeld S, Staub D, Hess C, Jaeger KA. Temporal artery compression sign--a novel ultrasound finding for the diagnosis of giant cell arteritis. Ultraschall Med. 2013Feb;34(1):47-50. doi: 10.1055/s-0032-1312821. Epub 2012 Jun 12

21. De Miguel E, Roxo A, Castillo C, Peiteado D, Villalba A, Martín-Mola E. The utility and sensitivity of colour Doppler ultrasound in monitoring changes in giant cell arteritis. Clin Exp Rheumatol. 2012 Jan-Feb;30(1 Suppl 70):S34-8. Epub 2012 May 10.

22. Pipitone N, Versari A, Salvarani C. Role of imaging studies in the diagnosis and follow-up of large-vessel vasculitis: an update. Rheumatology (Oxford). 2008 Apr;47(4):403-8. doi: 10.1093/rheumatology/kem379.

23.http://www.eular.org/myUploadData/files/1st%20International%20Workshop%20on%20US%20in%20LVV.pdf

24.http://www.danskreumatologiskselskab.dk/fileadmin/DRS/kliniskeretningslinjer/polymyalgia_rheumatica_og_arteritis_temporalis8.pdf

8. Appendix

Table 1: Ultrasound equipment settings

Vessel	Transducer	Depth	Colour Doppler frequency	PRF	Angle Colour Box	Colour Doppler Gain
AT,AF	18/15MHz Linear	minimum 1,5cm	7,5-10 MHz	2 Hz	60 degrees	In vessel lumen
AT,AF	18/15MHz Linear	minimum 1,5cm	7,5-10 MHz	2 Hz	60 degrees	In vessel lumen
AC,AA	14/15MHz* Linear	**	6,5-7,5 Mhz	3,5 Hz	60 degrees	In vessel lumen

* Can also be used a higher frequency transducer ** Depending of vessels depth

Table 2.Clinical and laboratory data collected at inclusion

Gender	Female___ Male____
Age	_____years
New occurred localized headaches	Yes___ No___
Artery Temporalis-tenderness on palpation	Yes___ No___
Artery Temporalis-reduced pulsation	Yes___ No___

Cord like hard thickening of temporal arteries is present	Yes___ No___
SR	mm
Positive TAB	Yes___ No___ Inconclusive___
Fulfilled ACR 1990 criteria (min. 3 out of 5)	Yes___ No___
CRP	mg/lt
Masseter/tongue claudicatio	Yes___ No___
sudden blindness/ (AION)	Yes___ No___
Amaurosis fugax	Yes___ No___
diplopia	Yes___ No___
other eye symptoms	Yes___ No___
Stroke/TCI	Yes___ No___
PMR symptoms	Yes___ No___
Arhritis	Yes___ No___
weight loss	Yes___ No___ If yes ____Kg
fever	Yes___ No___
fatigue	Yes___ No___
other relevant symptoms	
Initial CS dosis	_____mg
CS treatment duration prior to US examination	____days
CS treatment duration prior to TAB	_____days
UL guided TAB	Yes___ No___

Tabel 3: Six months evaluation

Alternative diagnosis. If Yes, write which:	Yes___ No___

Prompt effect of CS treatment	Yes___ No___
Cumulative CS dosis	mg
Ongoing CS dosis	mg
Relapse If yes choice one as minimum: 1) PMR ___ 2) cranial symptoms (headache, scalp tenderness, jaw claudication, cranial ischemic complications) ___ 3) systemic disease (fever, weight loss and increased inflammation markers without any other explanation) ____ 4) symptomatic large vessel involvement (extremity claudication) ____	Yes___ No___ If Yes number ____
Blindness after initiation of CS treatment	Yes___ No___
CS saving treatment If yes which:	Yes___ No___
Aneurism	Yes___ No___
Cancer	Yes___ No___

Table 4: US scanning results at baseline and at 6 months evaluation

	Vessel	Halo sign	Intima-Media complex in mm*	”compression sign” positive
1	AT ramus communis dx.	Yes___ No___	XXX	Yes___ No___
2	AT ramus parietalis dx	Yes___ No___	XXX	Yes___ No___
3	AT ramus frontalis dx	Yes___ No___	XXX	Yes___ No___
4	AF dx	Yes___ No___	XXX	Yes___ No___
5	AC communis dx	Yes___ No___		XXXXXXX
6	AA dx	Yes___ No___		XXXXXXX

7	AT ramus communis sin	Yes___ No___	XXX	Yes___ No___
8	AT ramus parietalis sin	Yes___ No___	XXX	Yes___ No___
9	AT ramus frontalis sin	Yes___ No___	XXX	Yes___ No___
10	AF sin	Yes___ No___	XXX	Yes___ No___
11	AC communis sin	Yes___ No___		XXXXXXX
12	AA sin	Yes___ No___		XXXXXXX