Today…

• Incidence of GCA and PMR
• Clinical manifestations of GCA and PMR
• How to make the diagnosis?
• Case discussions
• Treatment of PMR
• Treatment of GCA
  – Swedish rheumatology association guidelines for the treatment of GCA

Nomenclature of systemic vasculitis: "Definitions"
### Incidence of biopsy-proven giant cell arteritis and polymyalgia rheumatica in Sweden

<table>
<thead>
<tr>
<th>CHCC2012 name</th>
<th>CHCC2012 definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large vessel vasculitis (LVV)</td>
<td>Vasculitis affecting large arteries more often than other vasculitides. Large arteries are the aorta and its major branches. Any size artery may be affected.</td>
</tr>
<tr>
<td>Giant cell arteritis (GCA)</td>
<td>Arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries. Often involves the temporal artery. Onset usually in patients older than 50 years and often associated with polymyalgia rheumatica.</td>
</tr>
</tbody>
</table>
The Skåne region

Population: 1,344,689 (14% of the Swedish population)
Area: 11,035 km² (2.7% of area of Sweden)

The study area

Department of Pathology – Skåne

LUND
MALMÖ
HELSINGBORG
KRISTIANSTAD

Temporal artery biopsies in Skåne, 1997-2010

Incidence of Temporal Arteritis in Sweden 1997-2010

- Incidence per 100,000 ≥50 years:
  - Men: 7.7
  - Women: 19.6
  - All: 14.1

Table 1. Annual incidence rate of biopsy-proven giant cell arteritis in southern Sweden.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Age (years) at time of temporal artery biopsy median (IQR)</th>
<th>Incidence rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>840:75.5 (72.9-81.3)</td>
<td>14.1</td>
<td>13.1 to 15.0</td>
</tr>
<tr>
<td>Men</td>
<td>214:75.7 (72.0-81.6)</td>
<td>7.2</td>
<td>6.7 to 8.7</td>
</tr>
<tr>
<td>Women</td>
<td>626:76.0 (72.2-81.2)</td>
<td>19.6</td>
<td>18.1 to 21.1</td>
</tr>
</tbody>
</table>


Age specific incidence of GCA

The incidence increased with age.


[Graph showing age-specific incidence of GCA with periods 1, 2, and 3 indicated]
Incidence of polymyalgia rheumatica in Sweden

- Incidence of "pure" PMR (with no cranial symptoms of TA):
- 33.6/100,000 inhabitants in age group 50 yrs. and more
- Incidence rising with increasing age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 - 59</td>
<td>0</td>
<td>12.6</td>
<td>6.6</td>
</tr>
<tr>
<td>60 - 69</td>
<td>12.9</td>
<td>22.8</td>
<td>18.1</td>
</tr>
<tr>
<td>70 - 79</td>
<td>93.5</td>
<td>92.1</td>
<td>92.3</td>
</tr>
<tr>
<td>80 and older</td>
<td>53.2</td>
<td>6</td>
<td>34.4</td>
</tr>
</tbody>
</table>

Incidence of "pure" PMR: 58.3/100,000 inhabitants in age group 50 yrs. and more.

Temporal arteritis
Clinical presentations

- New onset headache
- Pain and stiffness (PMR-symptom)
- Visual disturbances
- Jaw claudication
- Scalp tenderness/temporal artery abnormalities
- Fever, anaemia, weight loss
- High inflammatory activities (ESR, CRP, thrombocytosis)

Polymyalgia rheumatica (PMR)
Clinical manifestations

- Pain and stiffness
  - Shoulders, neck, upper arm, pelvic girdle and thigh
  - Early morning symptoms
  - Tenderness but NO muscle weakness!
- General symptoms
  - Fatigue
  - Loss of appetite
  - Weight loss
  - Fever

Age above 50 yrs.
High ESR and CRP
Diagnosis of temporal arteritis

- Clinical features and laboratory analyses
- Temporal artery biopsy
- Imaging

Clinical phenotypes of GCA

Case – 1

74-year old woman
74-year old woman

- Christmas holiday 2018: new onset of "strange" occipital headache
  - Not responded to Paracetamol
- Few days later: Lt temporal headache, scalp tenderness, transient visual blurring (around one minute, no blindness)
- At the beginning of January -19:
  - Contact with primary health center: referred to physiotherapist
  - Consult physiotherapist (was chiropractor): message are given w/o help

- At the middle of January, new consultation to the GP
  - ESR: 58
  - Symptoms highly suggestive of GCA
  - Refer to the Rheumatology Clinic in Lund
- Rheumatology clinic (January 31):
  - Good general condition
  - Rt. temporal a.: positive pulses, non-tender
  - Lt. temporal a.: tender, dilated, weak pulse
  - Blood pressure: normal, equal bilateral
- Local exam.: no tenderness on arm or thigh muscles
  - ESR 74, CRP 100, HB 119, Plts 442

- Ultrasound of temporal arteries
  - Halo sign highly suggestive/diagnostic of temporal arteritis

- Treatment
  - Prednisolone 60 mg/day
  - Omeprazole 20 mg/day
  - Kalcipos-D 1x2

- Referral to ophthalmologist for assessment and TAB
Case – 2

75-year old woman

- Past medical history (PMH): recurrent venous thrombosis with PE 2009, Chronic Warfarin. Previous smoker
- June 2016: "Discomfort in chest and abdomen", dyspepsia, mild dyspnoea and palpitations
- Fatigue, loss of appetite, weight loss (6 kgs), high blood pressure

2016-10-13: admitted to hospital

- Recurrent abdominal pain/colic located under Rt and Lt hypochondrium and epigastric region.
- Lab.
  - Anaemia (Hb 111), leucocytosis (WBC 12.3) and thrombocytosis (plt 527).
  - ESR 97 mm/hr, CRP 46 mg/L
- Abdominal CT: cholecystolithiasis, no cholecystitis.
- Chest X-ray 2016-10-13: prominent descending aorta, measures 4.7 cm in lateral view with possible ectasia.
75-year old woman

- Re-exam of CT-abdomen: aortic wall thickness, aortitis?
  - What’s next?
  - CTA: consistent with aortitis, stenosis in coeliac trunk

CTA: 2016-10-13
75-year old woman

- Re-exam of CT-abdomen: aortic wall thickness, aortitis?
- What’s next?
- CTA: consistent with aortitis, stenosis in coeliac trunk
  - 2016-10-14: Prednisolone 60 mg.
- Rheumatology consultation: No arthritis. No PMR. No TA symptoms
- Further investigation?
- PET CT?
- Prednisolone discontinued after one day

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PET-CT (2016-10-20)
Extensive hypermetabolism in walls of thoracic and abdominal aorta, and in subclavian and carotid arteries bilaterally.

Treatment?

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75-year old woman

- Prednisolone 60 mg/day
- Metoject
- First follow-up 2016-12-13 (35 mg Prednisolone)
  - ESR 17, CRP 1.3. Doing well.
- Most recent follow-up visit 2018-02-08
  - CRP 2.9
  - Prednisolone 2.5 mg (to be discontinued)
  - Metoject 15 mg/week.
Case – 3

69-year old woman

• Retired assistant nurse, never smoked.
  • August 2017: pain in legs, knees, shoulders, neck and arms.
    Stiffness, fatigue, weight loss 5 kgs.
     – Referred to rheumatologist – February 2018
  • Have some headache mainly occipital and in the neck, no temporal headache. No visual symptoms, no jaw claudication.
  • ESR 93, CRP 100. RF and anti-CCP negative. Serum protein electrophoresis: severe inflammatory reaction, no M-component.

69-year old woman

• O/E: Tenderness over spinous processes in the neck, painful passive movement in shoulders. No arthritis. Tenderness on palpation of deltoid muscle insertion.
  – No temporal artery abnormality
• Diagnosis: Polymyalgia rheumatica (PMR)
  – Treatment: Prednisolone 30 mg/day for 10 days, gradually to be tapered to 15 mg/day in one month.
• Three weeks later: reduces Prednisolone on own initiative to 10 mg/day
69-year old woman

  - Headache (mainly frontal and around eyes) but also in the temporal area. New headache! No visual symptoms
  - On exam: weak pulses palpated on the temporal a. both sides.
    - Slight tenderness.
  - ESR 78 mm/hr., CRP 87 mg/L.
- What to do?
- Prednisolone increased to 40 mg/day.

69-year old woman

- Referred to ophthalmologist for temporal artery biopsy (TAB)
- TAB
  - muscular a. with infiltration of epithelioid multinucleated giant cells and lymphocytes in the tunica media, adventitial and intimal layers. Destruction of elastica interna. Features characteristic for GCA
  - Improved on Prednisolone 40 mg/day

69-year old woman

- Follow-up visits:
  - Headache recurred after Prednisolone tapered from 30 to 25 mg/day
  - Unable to taper Prednisolone, during beginning of August at 12.5 mg/day headache and recurrent short episodes of pain around the eyes.
  - CRP around 27-36 mg/L, ESR 58 mm/hr.
  - New information: patient has some kind of “inborn impaired vision”, bilateral cataract operation.
- What to do?
- Started on Tocilizumab 26th September, 2018, 162 mg sc/week
Treatment of polymyalgia rheumatica

2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative

Recommended treatment

Treatment of PMR

- Use the minimum effective individualized duration of GC therapy in PMR patients.
- Start dose: 12.5–25 mg prednisolone per day.
  - A higher initial prednisolone dose within this range in high risk of relapse and low risk of adverse events, whereas in patients with other risk factors for GC-related side effects, a lower dose may be preferred.
- Do not use initial doses ≤ 7.5 mg/day and definitely not >30 mg/day.
- Patients requiring high doses of GCs should be evaluated for alternate diagnoses and an alternate management plan.

Tapering schedule:

- A. Initial tapering: Taper dose to an oral dose of 10 mg/day prednisolone within 4–8 weeks.
- B. Relapse therapy: Increase oral prednisolone to the pre-relapse dose and decrease it gradually (within 4–8 weeks) to the dose at which the relapse occurred.
- C. Tapering once remission is achieved (following initial and relapse therapies):
  - Taper daily oral prednisolone by 1 mg every 4 weeks
  - Or by 1.25 mg decrements using schedules such as 10/7.5 mg on alternate days
Treatment of PMR

- Consider intramuscular (i.m.) methylprednisolone as an alternative to oral GCs. (120 mg methylprednisolone i.m. injection every 3 weeks)
- Use a single rather than divided daily doses of oral GCs for the treatment of PMR
- Considering early introduction of methotrexate (MTX) in addition to GCs, particularly in patients at a high risk for relapse and/or prolonged therapy (i.e. risk for comorbidities).
- No place for the use of TNFα blocking agents for treatment of PMR.

Guidelines for the investigation, treatment and follow-up of giant cell arteritis (GCA)

The purpose - why these guidelines?

• To summarize current principles for drug treatment of giant cell arteritis (GCA) based on:
  – Available evidence* in the literature
  – Consensus among the expert group selected by the Swedish Rheumatology Association

> The degree of evidence according to GRADE is stated as high, moderate, low or very low evidence

Glucocorticosteroids

• Oral
  – Prednisolone
    » Uncomplicated GCA (no visual symptoms or jaw claudication)
    – 40-60 mg/day

• I.V. pulse therapy
  » In case of serious ischemic manifestation as visual symptoms (amaurosis fugax, double vision...etc.)
  – Methylprednisolone: 1000 mg x 1 i 3 days


Prednisolone – suggested tapering regimen

• 40-60 mg Prednisolone/day for ≈ 4 weeks (normalisation of ESR and CRP and clinical improvement)
• Tapering
  – 10 mg every other week to 20 mg a day.
  – 2.5 mg every 2-4 weeks to 10 mg a day.
  – 1 mg every or every other month*
• Before each step in tapering check clinical symptoms and laboratory parameters (ESR and CRP) for relapse.
• In case of recurrence of signs and symptoms of active disease, bring the dose of Prednisolone to the step before.

* if no signs of relapse
Glucocorticosteroids
120 patients with GCA, 1950-1991

Table 1. Duration of glucocorticoid (GC) treatment in 120 patients with giant cell arteritis

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of patients in category</th>
<th>Duration of time to event median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose of GC, mg/dag</td>
<td>120</td>
<td>60 (10–160)</td>
</tr>
<tr>
<td>Time to reduc. to 7.5 mg/dag, month</td>
<td>115</td>
<td>8.5 (6–11.5)</td>
</tr>
<tr>
<td>Time to reduc. to 5.0 mg/dag, month</td>
<td>16</td>
<td>15.8 (9.1–24.4)</td>
</tr>
<tr>
<td>Time to reduc. to 2.5 mg/dag, month</td>
<td>7</td>
<td>23.6 (18.8–34.3)</td>
</tr>
<tr>
<td>Time to reduc. to 1.25 mg/dag, month</td>
<td>7</td>
<td>30.6 (19–54)</td>
</tr>
</tbody>
</table>

* Length of follow-up for entire group.

High age at diagnosis, high cumulative Prednisolone dose was associated with toxicities

Table 2. Remission rates and median daily dose of prednisone at 36, 52, and 78 weeks according to intervention

<table>
<thead>
<tr>
<th>Weeks treated</th>
<th>Prednisone dosage, median (IQR) mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.V. Methylprednisolone (MP) in GCA</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>IV GC</td>
</tr>
<tr>
<td>36 weeks</td>
<td>2 of 13</td>
</tr>
<tr>
<td>P</td>
<td>0.005</td>
</tr>
<tr>
<td>52 weeks</td>
<td>2 of 13</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
</tr>
<tr>
<td>78 weeks</td>
<td>4 of 12</td>
</tr>
<tr>
<td>P</td>
<td>0.008</td>
</tr>
</tbody>
</table>

* IQR = interquartile range; IV GC = intravenous glucocorticoid.

Arthritis & Rheumatism (Arthritis Care & Research) 49; 5, 2003, pp 703–708

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Biologics in treatment of GCA

- IL6 blockers (Tocilizumab)
- T-cell co-stimulator inhibitors (Abatacept)
- Anti-TNF alpha

Tocilizumab (TCZ) in GCA

- TCZ may be considered as a supplement to treatment with GCs in patients with pronounced clinical and laboratory inflammatory signs and high risk of side effects in future treatment with GCs
- The recommended dose of TCZ is 162 mg sc once a week
- In newly diagnosed patient, the effect of TCZ 162 mg every other week appears to be equivalent to the recommended dose(1)


Tocilizumab in GCA - treatment time, follow-up

- Treatment with TCZ should be stopped after 1 year in patients who achieved persistent remission
- Patients should be monitored by a specialist for at least 6 months after completion of treatment
- To enable follow-up of efficacy and safety of TCZ in clinical practice, all patients who start TCZ with the indication of GCA should be registered and followed in the Swedish Rheumatology Quality Register (SRQ)
### Prednisolon tapering regimen - according to the GIACTA-study

<table>
<thead>
<tr>
<th>Week</th>
<th>Prednisolone mg/dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7</td>
<td>Tapering from 20-60 mg to 20 mg after 7 weeks</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>12.5</td>
</tr>
<tr>
<td>10</td>
<td>12.5</td>
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<td>11</td>
<td>10</td>
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<tr>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
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</tbody>
</table>


### Tocilizumab is recommended as a supplement to treatment with Prednisolone in patients who meet ALL of the following criteria

1. GCA verified by biopsy or with imaging studies showing LVV (MRA, CTA, PET-CT)
2. Deterioration of symptoms during glucocorticoid (GC) therapy or relapse after treatment with GCs
3. Clinically active GCA
4. Current elevation of CRP and ESR
5. Obvious side effects of glucocorticoid treatment or great risk of such side effects from future treatment with glucocorticoids

This recommendation of the indication for TCZ is based on consensus in the Swedish Rheumatology Society.
Abatacept for GCA

• The addition of Abatacept to Prednisolone reduced the risk of relapse in GCA

• Abatacept may be considered as an alternative in cases of contraindication or serious AE of TCZ.


Methotrexate in GCA

• The addition of Methotrexate in treatment of GCA may be considered in late relapses without significant inflammatory activity, or with marked GC adverse effects, where the patient does not meet the indications for TCZ.


Acetylsalicylic acid (ASA) in GCA

• There is some evidence from retrospective observation studies that acetylsalicylic acid (ASA) and anticoagulants reduce the risk of ischemic complications, but there are no randomized controlled studies.

• The recommendation is to consider the use of ASA in GCA, if there are no contraindications.

Tack!