Marshallprotokollen

Norsk sarkoidoseforening
28. mai 2011

Inge Lindseth
4M-klinikken

Leting etter en mulig infeksions årsak har vært mislykket
Hvilken rolle spiller kroniske infeksjoner for sarkoidose?

Behandling av sarkoidose med Marshallprotokollen

1. Olmesartan
   Hovedmedisin

2. Anthocyanin
   Tilbyggeforbedring for ossete junkeader i perifere
Interesse for infeksjon ved sarkoidose

Basert på søk på Pubmed etter "infection AND sarcoidosis" og "sarcoidosis"
The results of the current study illustrate a demonstrable mycobacterial presence in sarcoidosis lesions suggesting an association between mycobacteria and some cases of sarcoidosis.

A patient with airway colonization from *P. aeruginosa* in the setting of idiopathic bronchiolitis (IB) mimicking diffuse panbronchiolitis (DPB) developed sarcoidosis. Impressive clinical and radiological improvement of both bronchiolitis and sarcoidosis features was achieved with a one-year treatment with low-dose erythromycin, thus suggesting a possible link between the two conditions in this specific case.
Together these results reveal that antigen-specific CD4+ and CD8+ T cells responses to multiple mycobacterial epitopes are present within sites of active sarcoidosis involvement, and that these antigen-specific responses are present at the time of diagnosis.
These results suggest that the immune response against indigenous \textbf{P. acnes} may play an important role in the pathogenesis of granuloma formation in a murine model. Mice were sensitized with heat-killed \textit{P. acnes} and complete Freund's adjuvant and were subsequently challenged with heat-killed \textit{P. acnes} at 9-week intervals. \textit{P. acnes} challenged mice developed epithelioid cell granulomas in the lungs. These mice showed a pulmonary immune response characterized by an increased number of T-lymphocytes, especially CD4- cells, and the ratio of (CD4 - CD8)- to (CD8+ - CD8-) was increased. Furthermore, significant elevations in both angiotensin-converting enzyme (ACE) serum levels and antibodies against \textit{P. acnes} were observed. Mice sensitized with \textit{P. acnes} without complete Freund's adjuvant were capable of forming granulomatous lesions, which appeared to be caused by indigenous \textit{P. acnes}. The genome of \textit{P. acnes} was found in the lungs, hilar lymph nodes, liver, and spleen in non-sensitized mice, which were thought to be gone from. These results suggest that the immune response against indigenous \textit{P. acnes} may play an important role in the pathogenesis of granuloma formation in a murine model.

\textbf{Propionibacterium acnes} is the most common bacterium commensal in peripheral lung tissue and mediastinal lymph nodes subjects without sarcoidosis. These results suggest that \textit{P. acnes} normally resides in peripheral lung tissue and mediastinal lymph nodes and that the strains of \textit{P. acnes} isolated from sarcoid lymph nodes were not specific to sarcoidosis.

\textbf{Abstract}

\textbf{Background}\n
\textit{Propionibacterium acnes} is the most common bacterium commensal in peripheral lung tissue and mediastinal lymph nodes subjects without sarcoidosis. In many sarcoidosis patients, \textit{P. acnes} is isolated from sarcoid lymph nodes and the hypothesis that \textit{P. acnes} may play an important role in the pathogenesis of sarcoidosis has been made.

\textbf{Method}\n
\textit{Methods} used in this study included cultivation of lymph node biopsies from sarcoidosis patients along with a comparative analysis of sarcoidosis and control patients.

\textbf{Results}\n
\textit{Propionibacterium acnes} were isolated in 18 out of 18 sarcoid lymph nodes of sarcoidosis patients. However, in 10 out of 10 control lymph nodes, \textit{P. acnes} were not isolated. Furthermore, \textit{P. acnes} isolated from sarcoid lymph nodes were also isolated from peripheral lung tissue specimens of sarcoidosis patients.

\textbf{Conclusion}\n
These results suggest that \textit{P. acnes} normally resides in peripheral lung tissue and mediastinal lymph nodes and that the strains of \textit{P. acnes} isolated from sarcoid lymph nodes were not specific to sarcoidosis.
Detection of 'Borrelia-like' organisms by FFM in tissue sections of CS underlines the possibility that such microorganism may be involved in the pathogenesis of some cases of CS.

The hypothesis of causality between a B. burgdorferi infection and sarcoidosis cannot be confirmed by this data.
These results support the hypothesis that rickettsiae may contribute to a granulomatous process, as is seen in sarcoidosis.

In conclusion, we could not find evidence to support the primary hypothesis of the study, that a rickettsial infection should be involved in the pathogenesis of sarcoidosis.
Ikke noe nytt….

- **HIV kan føre til/øke risikoen for:**
  - Bakterielle sykdommer: tuberkulose, sepsis, lungebetennelse
  - Protozosykkdommer: toxoplasmose, mikrosporidiose, kryptosporidiose, isopsoriasis, leishmaniasis
  - Soppsykkdommer: PCP, candidasis, kryptokokkosis og pencillinose
  - Virussykkdommer: CMV, herpes simpleks og herpes zoster
  - Kreft: Kaposi sarkom, lymfom, skiveepitelscarsinom

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1. Mikroorganismen må finnes i stort antall hos alle organismer som lider av sykdommen, men bør ikke finnes hos friske.
2. Mikroorganismen må bli isolert fra en som har sykdommen og deretter bli dyrket i et vekstmedium.
3. Den dyrkete organismen bør forårsake sykdom når en frisk organismen blir eksponert for den.
4. Mikroorganismen må igjen bli funnet i den som ble eksponert for mikroorganismen og bli identifisert som identisk med den opprinnelige, spesifike mikroorganismen.

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**Kochs postulater**
- Lang inkubasjonsperiode
- Vanskelig å dyrke/påvise mikroorganismene
Discussion
Acid fast organisms were grown successfully from the blood of 19 of 20 patients with active sarcoidosis, whereas no organisms were grown from the blood of 20 controls. Findings of variable size, predominantly coccoid forms, larger L forms, and short acid fast rods suggested that the organisms were CWDF of mycobacteria. It has previously been established
A patient with suspected sarcoidosis died from miliary tuberculosis. Pulmonary tuberculosis with cutaneous aspects of sarcoidosis, tuberculosis or both? Tuberculosis and sarcoidosis: The continuing enigma.


"Ikke-sarkoidosepasienter"

1,2 % hadde vært i nær kontakt med andre med sarkoidose før diagnosen (arbeidskolleger, nære venner og samme husholdning)

Sarkoidosepasienter

40 % hadde vært i nær kontakt med andre med sarkoidose før diagnosen (arbeidskolleger, nære venner og samme husholdning)

Hip joint microbiome


<table>
<thead>
<tr>
<th>Organism</th>
<th>% Composition of 118 clones sequenced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysobacter</td>
<td>44.1%</td>
</tr>
<tr>
<td>Unidentified bacterial clones</td>
<td></td>
</tr>
<tr>
<td>Stenotrophomonas</td>
<td></td>
</tr>
<tr>
<td>Gamma proteobacterium</td>
<td></td>
</tr>
<tr>
<td>Hydrothermal vent eubacterium</td>
<td></td>
</tr>
<tr>
<td>Methylobacterium</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus</td>
<td></td>
</tr>
<tr>
<td>Proteus</td>
<td></td>
</tr>
<tr>
<td>Iron-oxidizing lithothroph ES-1</td>
<td></td>
</tr>
<tr>
<td>Bradyrhizobium</td>
<td></td>
</tr>
<tr>
<td>Bacteroides</td>
<td></td>
</tr>
<tr>
<td>Methylobacteriaceae family</td>
<td></td>
</tr>
<tr>
<td>Acidobacteria</td>
<td></td>
</tr>
<tr>
<td>Eubacterium</td>
<td></td>
</tr>
<tr>
<td>Endophytic bacteria</td>
<td></td>
</tr>
<tr>
<td>Xylella</td>
<td></td>
</tr>
</tbody>
</table>
Lungemikrobiom

- Scientists are even discovering ecosystems in our bodies where they weren’t supposed to exist. Lungs have traditionally been considered to be sterile because microbiologists have never been able to rear microbes from them. A team of scientists at Imperial College London recently went hunting for DNA instead. Analyzing lung samples from healthy volunteers, they discovered 128 species of bacteria. Every square centimeter of our lungs is home to 2,000 microbes.

New York Times juli 2010

Karveggen

Human oral, gut, and plaque microorganisms in patients with atherosclerosis

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Periodontal disease has been associated with atherosclerosis, suggesting that bacteria from the oral cavity may contribute to the development of atherosclerosis and cardiovascular disease. Furthermore, the gut microbiota may affect obesity, which is associated with atherosclerosis. Using PCR, microarray data, and 16S rDNA sequencing, we studied the microbial composition of atherosclerotic plaques and found that DNA from the oral microbiome was present in atherosclerotic plaques. To investigate the role of the oral microbiome in atherosclerosis, we used microbiota transplants to test the hypothesis that the oral microbiome may contribute to atherosclerosis in humans. In a study of 15 patients with atherosclerosis, and oral squamous cell carcinoma, we found that the oral microbiome was present in atherosclerotic plaques, and that the oral microbiome was present in atherosclerotic plaques.
Within the body of a healthy adult, microbial cells are estimated to outnumber human cells by a factor of ten to one. These communities, however, remain largely unstudied, leaving almost entirely unknown their influence upon human development, physiology, immunity, and nutrition. To take advantage of recent technological advances and to develop new ones, the NIH Roadmap has initiated the Human Microbiome Project (HMP) with the mission of generating resources enabling comprehensive characterization of the human microbiome and analysis of its role in human health and disease.

Traditional microbiology has focused on the study of individual species as isolated units. However many, if not most, have never been successfully isolated as viable specimens for analysis, presumably because their growth is dependant upon a specific microenvironment that has not been, or cannot be, reproduced experimentally. Among those species that have been isolated, analyses of genetic makeup, gene expression patterns, and metabolic physiologies have rarely extended to inter-species interactions or microbe-host interactions. Advances in DNA sequencing technologies have created a new field of research, called metagenomics, allowing comprehensive examination of microbial communities, even those comprised of uncultivable organisms. Instead of examining the genome of an individual bacterial strain that has been grown in a laboratory, the metagenomic approach allows analysis of genetic material derived from complete microbial communities harvested from natural environments. In the HMP, this method will complement genetic analyses of known isolated strains, providing unprecedented information about the complexity of human microbial communities.
Hvor farlig er sarkoidose?

Access-studien

- Sarkoidosepasienter fulgt i to år
- Ingen kategori for "frisk", bare "forbedret"
- De fleste (80%) hadde enten uforandret tilstand eller blitt verre

Two year prognosis of sarcoidosis: the ACCESS experience

- 74% av dem som starter prednisolonbehandling får tilbakefall av sykdommen (de fleste 2 – 6 måneder etter avsluttet prednisolon)

Outcome in Sarcoidosis*

The Relationship of Relapse to Corticosteroid Therapy

- Studieobjective: At determine the demographic, clinical, and radiographic characteristics of patients with sarcoidosis who relapsed after achieving clinical remission following a period of stable, low-dose corticosteroid therapy
- Patients and methods: 100 patients with sarcoidosis were prospectively enrolled in a cohort study. The patients were divided into four groups: (1) patients who relapsed during corticosteroid therapy, (2) patients who relapsed during corticosteroid withdrawal, (3) patients who relapsed during corticosteroid discontinuation, and (4) patients who remained in remission.
- Results: During the follow-up period, 100 patients with sarcoidosis were prospectively enrolled in a cohort study. The patients were divided into four groups: (1) patients who relapsed during corticosteroid therapy, (2) patients who relapsed during corticosteroid withdrawal, (3) patients who relapsed during corticosteroid discontinuation, and (4) patients who remained in remission.
1

Olmesartan

Hovedmedisin

2

(Antibiotika)

Tilleggsbehandling for enkelte pasienter i perioder
The Use of Tetracyclines for the Treatment of Sarcoïdosis

Aisha Bhatti, MD, PhD; Armita Foroe, MD; Javier Casabure, MD;
Alexandre Kazishten, MD; Louis Daherine, MD

Background: To evaluate the safety and efficacy of tetracyclines in the treatment of sarcoidosis, a retrospective, open-label study was performed in patients with sarcoidosis.

Observations: Twelve patients with extensive sarcoidosis were treated with tetracycline, 200 mg, on a median duration of 12 months. Three patients had an exacerbation in the 3rd month of the study. The median follow-up was 26 months. A clinical improvement was observed in 30 patients, consisting of complete resolution of skin lesions in 1 patient and significant improvement in another patient. Adverse effects were minimal, including 5 patients, who developed hyperglycemia. A slight hyperglycemia occurred in 2 patients at the time of previous lesions, which completely disappeared after monotherapy was discontinued. A relapse of hyperglycemia occurred in 2 patients, who were treated with dexamethasone, 0.1 mg, followed by complete remission of diabetes.

Conclusions: These results support that tetracycline and azathioprine may be beneficial for the treatment of sarcoidosis. Randomized controlled studies are warranted to confirm these preliminary findings in the treatment of tetracyclines in these patients.

Sarcoidosis is a granulomatous, multisystem disorder that involves predominantly the lungs and lymph nodes, but can affect any organ system. The disease is characterized by the formation of non-caseating epithelioid granulomas.

Olmesartan er…

- En blodtrykksmedisin
- Ikke et antibiotikum, men en stimulator av immunsystemet
- En stimulator av det uspesifike immunsystemet, særlig viktig for forsvaret mot intracellulære bakterier
- Stimulerer gjennom Vitamin D-reseptoren (VDR)
Antimikrobielle Peptide

Olmesartan

Human Immunodeficiency Virus (HIV)
- completely overtakes the VDR

Borreliaburgdorferi
- Live Bb downregulates the VDR 50 fold
- Lysed Bb downregulates the VDR 8 fold

Stoff laget av bakterier og virus som blokkerer reseptoren

Hvordan virker olmesartan?

Olmesartan

Cannabinoid-reseptor 1
- GABA
- AMP (Cathelicidin osv)
- TLR

Vitamin D-reseptor
- CYP24A1
- MTSS1
- NOD2

All-reseptor(antagonist)
- NADPH-oksidase
- NF-kappa B
- Superoksid
- TNF-α
Olmesartan og
benvevet/hyperkalsemi/vitamin D

Er Olmesartandosene på MP trygge?

**FDA har ikke satt noe øvre dosegrense**

"CS-866 [olmesartan] var trygt og godt tolerert i doser opp til 160 mg/dag.... [Olmesartan] gir ingen alvorlige bivirkninger."


"Resultatene fra kliniske studier på mer enn 3000 pasienter som har brutt olmesartan [2,5 – 80 mg] viser at bivirkningene generelt var lik placebo og ikke relatert til dose."

Antibiotika?

- Bredspektret antibiotika (minocyclin, clindamycin, azitromax)
- Små og pulserte doser (dosene justeres i takt med symptomer)
- Ikke absolutt nødvendig på MP

Ingen rask og symptomfri behandling....

**Immunpatologi**
Symptomer som oppstår som følge av at mikroorganismer drepes/immunsystemet aktiveres
Immunpatologi er velkjent fra andre sykdommer

- HIV
- Borrelia (flåttsykdom)
- Tuberkulose
- Lungebetennelse
- Syfilis

Immunpatologi

Feilaktig bruk av medisiner på Marshallprotokollen kan gi kraftige immunpatologireaksjoner
Symptomnivå

% bedring i helsetilstand/reduksjon i symptomnivå

Pasient 1
Pasient 2
Pasient 3

Symptomregistrering (eksempel)

<table>
<thead>
<tr>
<th>Symtom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undcape</td>
<td>8</td>
</tr>
<tr>
<td>Energi om morgenen/utvalhet</td>
<td>9</td>
</tr>
<tr>
<td>Konstradigonen</td>
<td>3</td>
</tr>
<tr>
<td>Surrere/svæpning/horing/lit imkontroll på hvem som kommer ut av munn</td>
<td>3</td>
</tr>
<tr>
<td>&quot;Ubeklagelig følelse&quot; i magen, men ikke diare eller forstoppelse</td>
<td>5</td>
</tr>
<tr>
<td>Unormal grepighet etter fysisk aktivitet</td>
<td>6</td>
</tr>
<tr>
<td>Ecology for sorn i løpet av dagen</td>
<td>6</td>
</tr>
<tr>
<td>Kroppevekt</td>
<td>3 (for lav)</td>
</tr>
</tbody>
</table>

Utarbeidet av Inge Lindseth ved 4MV-klinikken oktober 2010
Kosthold, lys…

Pasienteksempel

• Mann født i 1954
• Første konsultasjon hos oss: 17.04 2008
• Diagnostisert med sarkoidose i 2002 (grad II med fibrose)
• Medisiner:
  Inntil 30 mg predinsolon daglig siden diagnosen,
  Fosamax, Calcigra
• Søvnløshet, lite energi
• Hepatitt C
• 25-hydroksyvitamin D: 76
• 1,25-dihydroksyvitamin D: 111
• ACE: 195
• Røyker 2-4 sigaretter hver dag, har røyet siden 25-årsalderen
• Uttalelse fra pasienten før oppstart:
  "Æ føle mæ egentlig ikke så dårlig,
  e trøtt og sliten, men er ikke hemmet av
  lungefunksjonen"
Behandlingsforløp

- Sluttet med prednisolon jan 2008
- Startet med Olmetec i mai 2008
- Oppstart minocyclin juli 2008
- Full dose minocyclin november 2008
- Oppstart kombinasjon minocyclin og azitromax november 2008.
- Oppstart med kombinasjon av tre ulike antibiotika (clindamycin i tillegg) mai 2009
- Full dose av alle antibiotika november 2009
- Pause/avsluttet alle antibiotika februar 2010
- Fortsetter fortsatt med Olmetec i dag

Utvikling i blodprøver

Legens notat: "Utrolig positiv endring i leverparametrene"  
Legens notat: "Har ikke lenger hodepine og smerter i foten.  
Legens notat: "Har ikke lenger drap frå hilusler.  

(ALAT; ASAT = "leverprøver")
Utvikling i blodprøver

Pasienteksempel 2

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Gradering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piper i begge når jeg ligget nede</td>
<td>7</td>
</tr>
<tr>
<td>Desig, selvsagt</td>
<td>8</td>
</tr>
<tr>
<td>Kræmende nøk vel høyere aktivitet</td>
<td>8</td>
</tr>
<tr>
<td>Konstant syromfølelse</td>
<td>10</td>
</tr>
<tr>
<td>Klar i hånden når jeg snakke</td>
<td>6</td>
</tr>
<tr>
<td>Hosier</td>
<td>9</td>
</tr>
</tbody>
</table>
En måned senere

- **Hverdagsprotokoll**: med graden av 0-10 (hvor 0-10 er skadelig) og noen ganger overhodet i noen for alvor forvirret. Senere symptomer som eventuelt har vært evne til å gi kortfølelse og eventuelt nye symptomer. Ved første gangs utstyring har de begynnelsen til 6-7 symptomer.

<table>
<thead>
<tr>
<th>Symptomer</th>
<th>Grad</th>
<th>andommet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poper i ogset, når jeg ligger ned</td>
<td>0-1</td>
<td>4</td>
</tr>
<tr>
<td>Selvstens av i hver enigg, tett</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Femade menre ved lyse aktivitet</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Konstant sykestifteelse</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Klev i halsen når jeg snakker</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Helse</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hodepine på et heltent-punkt</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Utarbeidet av AM-Kliniken 2009, oppdatert september 2010

**Hvor lang tid tar protokollen?**

**Hvor lang tid tar det før man føler seg klart bedre mesteparten av tiden?**
In 2005, this father of seven could hardly breathe and suffered from intense joint pain. Exhausted and sore, he found it extremely difficult to walk up the stairs. Now, after about 2 1/2 years on Autoimmunity Research Foundation’s Marshall Protocol he's essentially pain and symptom free and is back to digging trenches in his garden. Today his sarcoidosis has largely resolved and he's been cancer free for over a year.

Several years ago this West Virginia native feared for his life. He had managed to survive two heart attacks, but his sarcoidosis of the heart, myopathy, atrial fibrillation, and fluid-filled lungs were only getting worse. Now, after 2 1/2 years on Autoimmunity Research Foundation’s Marshall Protocol, this 69-year old is active again thanks to the fact that his heart conditions and sarcoidosis symptoms have improved considerably.

Well, the MP literally cured ALL my health problems. Before starting the MP I had no idea that all my symptoms were connected and were all the result of bacterial infection. So it was a real eye opener when all my symptoms responded to the treatment. So although I started the MP for sarcoidosis, it fixed everything else as well…a real bonus! My experience certainly discounts the torpedo theory – the idea that each health problem needs to be solved with a different intervention.