Pulmonary Sarcoidosis
A Holistic Approach

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Outline

• Overview and epidemiology
• Presentations and diagnosis
• Management
• Challenges
Sarcoidosis: What is it?

- Chronic multisystem disorder (affects lungs in >90%)
- 1877: described by Jonathan Hutchinson
- Unknown aetiology
- Typically non-caseating granulomas (organised collections of activated macrophages and T cells) in affected organs with distortion of normal architecture
- Pulmonary sarcoidosis second most common respiratory disease in adults aged < 40

No single diagnostic test
No single test for monitoring disease activity
Immunopathology

• Mechanisms of granuloma formation not well understood
  • Exposure to unknown antigen
  • Acquired cellular immunity directed against antigen (APCs and antigen-specific lymphocytes)
  • Immune effector cells promote non-specific inflammatory response

• Fibrotic response can cause irreversible organ damage

• TNFα and IL8 implicated in chronic sarcoidosis

Baughmann RP et al Sarcoidosis Lancet 2003
Epidemiology

- ‘Adults aged 20-40 years’
- Prevalence difficult to establish: often asymptomatic
- UK incidence 10-20 per 100,000
- More prevalent in Blacks and Afro-Caribbeans
- Blacks and Afro-Caribbeans have more severe disease and higher risk of extra-pulmonary manifestations
ACCESS: Age distribution by gender

A Case Control Etiological Study of Sarcoidosis

Figure 1. Distribution of patients with sarcoidosis by age at diagnosis and sex. The percentages of male and female patients are shown separately. ■ Male; □ Female.

Baughman et al Am J Respir Crit Care Med 2001
ACCESS: Disease patterns and QoL

- Sarcoidosis clusters in families
- Low income predicts poorer outcome
- Organ involved differs with race, sex + age
- Industrial exposures associated with ↑ risk

- Diagnosis often late: symptoms attributed to other causes
- Impaired lung function and/or SOB linked to poor QoL
Extra-pulmonary presentations

- **Neurology**
  - Peripheral neuropathy
  - Meningitis
  - Cranial nerve palsy
  - S.O.L.
  - Transverse myelitis
- **ENT**
  - Uveitis
  - Conjunctivitis
  - Sjogren-like syndrome
- **Dermatology**
  - Erythema nodosum
  - Plaques
- **ENT**
  - Nasal granuloma
  - Laryngeal plaques
- **Rheumatology**
  - Polyarthritis
  - Bone cysts
- **Rheumatology**
  - Polyarthritis
  - Bone cysts
- **Respiratory**
  - Hypercalcemia
  - Hypercalcuria
  - Renal failure/calculi
  - Lymphadenopathy
  - P.U.O.
- **General Medicine**
  - Cardiology
  - Conduction disorders
  - Myocarditis
- **General Medicine**
  - Cardiology
  - Conduction disorders
  - Myocarditis
- **Ophthalmology**
  - Hepatosplenomegaly
  - Salivary gland enlargement
- **Gastroenterology**
  - Hepatosplenomegaly
  - Salivary gland enlargement
Classic acute presentations

- Lofgren’s syndrome
  - Erythema nodosum
  - Polyarthritis
  - BHL on CXR

- Heerfordt’s syndrome
  - Fever
  - Parotid enlargement
  - Anterior uveitis
  - Facial nerve palsy
Pulmonary presentations

- Cough, usually non-productive
- Breathlessness, usually on exertion
- Chest tightness and/or pain
- Systemic upset: sweats, fevers, malaise, fatigue, weight loss
- Insidious onset associated with poorer prognosis
- Bilateral hilar lymphadenopathy
- Pulmonary infiltrates or fibrosis
Important differential diagnoses

- **BHL**
  - TB, lymphoma
  - bronchogenic carcinoma, pulmonary hypertension

- **BHL + pulmonary infiltrates**
  - TB, pulmonary eosinophilia, lymphangitis

- **Diffuse pulmonary infiltration**
  - rheumatoid lung, IIPs, hypersensitivity pneumonitis

- **Non-caseating granulomas**
  - TB, lymphoma, hypersensitivity pneumonitis, berylliosis

*Sarcoidosis is a diagnosis of exclusion*
Initial investigations

- FBC, bone and liver profile
- ACE (raised in 2/3)
- Immunoglobulins
- 24 hour urine calcium
- Tuberculin skin testing*
- T cell based blood tests (ELISpot, Quantiferon)*
- CXR
- HRCT
- $^{18}$F FDG Positron emission tomography (PET)
- $^{67}$Gallium

* Use in endemic regions limited by higher background rates of latent TB. Reduces value of positive tests, but negative tests (less frequent) more useful to exclude TB
Chest radiograph staging (Scadding)

- BHL 50%
- Normal 5%
- Fibrosis 5%
- BHL + infiltrates 25%
- Infiltrates only 15%

Legend:
- Stage 0
- Stage I
- Stage II
- Stage III
- Stage IV
Further investigations

- Lung function: may be normal despite widespread radiographic abnormalities
- May be abnormal with normal CXR
- Classically restrictive spirometry with reduced gas transfer
- Airflow obstruction not uncommon

- Bronchial washings and BAL
- Endobronchial biopsies yield diagnosis in up to 40%; transbronchial biopsies have higher yield: 4 biopsies needed
- Send biopsies in saline for culture
- EBUS-TBNA now method of choice if lymphadenopathy: better yield
Course of disease

- Variable
- High rate of spontaneous remissions
- Potential for late relapses (average 30%)
- Overall:
  - remission in > 50% within 3 years
  - remission in 2/3 within 10 years
  - persistent disease in 1/3

Iannuzzi MC, Fontana JR JAMA 2011
Treatment

• Corticosteroids first line
• Beneficial effects first reported in 1950s
• Widely used since 1960s
• Who, when to treat and how long: controversial

• Unclear whether steroids prevent lung fibrosis or improve long-term survival
• Many trials included stage I disease patients who often show spontaneous resolution without treatment
Steroid treatment protocols
controlled studies

• Initial daily dose of prednisolone 30-60mg
• Reduce each month according to response
• Average 10mg daily for 6-12 months before attempting gradual withdrawal
• Clinical observation suggests continue for 2 years to help prevent relapses
• Consider alternate day dosing when stable

Axelrod L Medicine 1976
Spratling L et al Chest 1985
Inhaled steroids

- Open label study reported benefit in 1986
- Only 2 later studies showed benefit (as first line therapy or maintenance after response with oral steroids)
- Not recommended routinely
- Consider for cough; role in maintenance unclear

Selroos O Ann NY Acad Sci 1986
Erkkila SD et al Sarcoidosis 1988
Alberts C et al ERJ 1995
How/when do we measure response?

• No single marker of disease activity
• Symptoms
• Examination (nodes, rash, ptosis, nodules...)
• Pathology: ACE, ESR, CRP, biochemical or haematological abnormalities
• Radiology: infiltrates, nodularity ± nodes
• Physiology: lung function
• Every 3-12 months depending on treatment/stability
Side-effects of oral corticosteroids

• Weight gain, fluid retention
• Moon face, buffalo hump
• Hypertension
• Mood swings
• Osteoporosis
• Impaired glucose tolerance and diabetes
• Increased susceptibility to infection
British Thoracic Society
ILD Guidelines

• Studies of long-term benefits of steroids inconclusive. Given high rate of spontaneous remission and significant side-effects, treatment not indicated for:
  • asymptomatic stage I disease
  • asymptomatic stage II or stage III disease with mildly abnormal lung function and stable disease over 3-6 months
British Thoracic Society
ILD Guidelines

• Consider treating for at least 12 months if:
  • deteriorating lung function over 3-6 months
  • deteriorating radiological changes
  • significant pulmonary symptoms of cough, shortness of breath, chest pain or haemoptysis
What about steroid unresponsive patients?

- Sarcoid *does* respond to steroids
- The issue is the dose required
- If daily long-term dose of prednisolone is > 10-15 mg od, need to consider adding in one or more alternatives
- The aim is to reduce steroid dose to limit side-effects
Alternatives to steroids in pulmonary sarcoidosis

- Methotrexate
- Hydroxychloroquine
- Azathioprine
- Infliximab
- Etanercept

- Thalidomide
- Cyclosporin A
- Chlorambucil
- Leflunomide
- Pentoxifylline

1 RCT of MTX; 3 of chloroquine
Fatigue in sarcoidosis

• Reported in 50-70%; may be severe
• Associated with significantly impaired QoL
• Cause unclear and probably multifactorial:
  • granuloma formation; cytokine release especially TNF α
  • treatment(s)
  • depression, anxiety, altered sleep patterns
• Not always obviously correlated with disease activity
• Association with small fibre neuropathy
• May be correlated with activity on $^{18}$FDG-PET

Drent M, Lower EE, de Vries J *ERJ* 2012
Measuring fatigue

Fatigue Assessment Scale (FAS): 10 questions validated in sarcoidosis

<table>
<thead>
<tr>
<th>Statement</th>
<th>Never</th>
<th>Sometimes</th>
<th>Regularly</th>
<th>Often</th>
<th>Always</th>
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<tbody>
<tr>
<td>I am bothered by fatigue</td>
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<td>I get tired very quickly</td>
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<td>I don't do much during the day</td>
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<td>I have enough energy for everyday life</td>
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<td>Physically, I feel exhausted</td>
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<td>I have problems starting things</td>
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<td>I have problems thinking clearly</td>
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<td>I feel no desire to do anything</td>
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<td>Mentally, I feel exhausted</td>
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<td>When I am doing something, I can concentrate quite well</td>
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Min 10; max 50; score > 22 indicates substantial fatigue; change of 4 points significant

De Kleijn WP et al Respir Med 2011
www.ildcare.nl
Managing fatigue

• Treat reversible causes:
  • metabolic abnormalities (thyroid, diabetes, anaemia)
  • psychosocial conditions
  • treatment related fatigue
  • sleep disturbance including obstructive sleep apnoea (obesity, upper airway granulomas)
• Consider neuro-stimulants (e.g. methylphenidate)
• Hydroxychloroquine negatively associated with fatigue

de Kleijn WP et al Sarcoid Vasc Diffuse Lung Dis 2009
Neurostimulants in sarcoid-related fatigue

• Open label trial of methylphenidate:
  • 4 of 5 patients reported improved fatigue
  • no objective measurements of fatigue

• Double blind placebo controlled cross-over study of D-methylphenidate (n=10):
  • significant improvement after 4 weeks
  • mean change of 4.5 points on FAS

• Double blind cross-over study of armodafinil:
  • significant improvement

Wagner MT et al Sarcoïd Vasc Diff Lung Dis 2005
Lower EE et al Chest 2008
Baughman RP et al Chest 2009
Step wise approach to fatigue

Good control of disease?

No

Maximise therapy

Yes

Evaluate for co-existing disease

Check glucose, thyroid function

Treat co-existing disease

Evaluate for sleep apnoea and/or depression

Consider neurostimulant if fatigue persists

Adapted from Drent M et al ERJ 2012
Exercise and PR: now

- Limited data
- Retrospective study in patients undergoing pulmonary rehab 2006-2012; measured parameters before + after:
  - 6 MWT
  - quadriceps peak torque (QPT)
  - symptom checklist (SCL 90 score)
  - short form health survey (SF36)
- 11/20 showed ↑ 6MWT (mean ↑ 88 m)
- 10/20 showed ↑ QPT to almost normal
- Majority had improved SF36 and ↓ SLC 90 scores

De Heer M ERJ 2013
Exercise and PR: the future

• Ongoing RCTs in France, Norway and Germany
• CBT and graded exercise programmes effective in chronic fatigue
• ? role of high intensity interval training

White PD, Goldsmith KA, Johnson AL et al Lancet 2011
Shiraev T, Barclay G Aust Fam Phys 2012
• UK ‘fattest’ country in Europe: 26% now obese
• Obese people 80 x more likely to develop type 2 DM than those with BMI 22
• Obesity predisposes to heart disease and cancer
• Diabetes increases risk of coronary artery disease up to 7 fold
• Diabetes accounts for 10% of NHS budget

www.diabetes.co.uk
Low fat diets and obesity

Proportion of American adults who are obese has doubled over past 30 years from 15% to 34%

www.ncbi.nlm.nih.gov/books/NBK19623/
Carbohydrate intake and weight loss

‘Overweight people need to reduce starches and sugar in order to lose weight and remain healthy’

Osler W The Principles and Practice of Medicine reprinted 1978
Dietary fat and heart disease

- Fat accounts for 40% of energy supply in diet in Belgium, Cyprus, France, Spain and Switzerland
- Increasing data suggest that dietary saturated fat intake is not clearly linked to coronary heart disease
- Meta-analyses suggest low carbohydrate, high fat diets are more effective in inducing weight loss and improving cardiovascular risk factors than low fat, high carbohydrate diets

WHO European Cardiovascular Disease Statistics 2012
Hession M et al Obes Rev 2009
Dietary advice

• Avoid refined foods whenever possible
• Avoid added sugar (biscuits, cakes, spreads...)
• Limit starchy carbohydrates (potatoes, rice, pasta, bread) and fruits high in sugar
• Focus diet on good quality meat and fish, green vegetables and salads
• Include some cheese, eggs and healthy fats (avocados, nuts, olive oil, butter, coconut oil)
• Use caution in diabetic patients on insulin
British Thoracic Society Sarcoidosis Registry

- Open to all UK-based respiratory physicians
- 244 records submitted Jan 2013-Jul 2016
- Providing unique insights into referral patterns, presentation, mode of diagnosis and management of UK patients with pulmonary sarcoidosis
- Highlighting need for education to reduce delays in diagnosis; need for access to EBUS-TBNA in secondary care; frequency of co-morbidities; and need for new clinical trials

Coker RK et al ERS 2016
Summary

• Sarcoidosis is a diagnosis of exclusion
• No single diagnostic test
• No single marker of disease activity
• Steroids are mainstay of treatment for vital organ involvement
• Attention to co-morbidity and treatment side-effects essential to improve quality of life
• UK Registry data should help improve diagnosis, management and access to clinical trials
Thank you