Diagnoses of Chronic Beryllium Disease within Cohorts of Sarcoidosis Patients

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Introduction

• There is no Beryllium production in Germany.
• Therefore, an occupational surveillance programm does not exist and in occupational medicine chronic beryllium disease is only rarely diagnosed.
• Beryllium lymphocyte proliferation test is not used on a routine basis.
Introduction

• In a dental technician suffering from chronic corticosteroid resistant sarcoidosis we corrected the diagnosis in Chronic Beryllium Disease by proof of exposure and demonstrating sensitisation by means of skin testing.

• This led us to the hypothesis that CBD cases are hidden in the cohort of sarcoidosis patients.
Chronic Beryllium Disease

at manifestation
w/o symptoms

plus 18 years
at diagnosis

Müller-Quernheim et al. 1996
Intracutaneous Beryllium Skin Test

0.1 ml of 0.05 0.01 0.005% BeSO₄ s.c.

4 days

28 days

Müller-Quernheim et al. 1996
Intracutaneous Beryllium Test

Histological characteristics of macroscopically positive tests in 10 patients with CBD (positive BeLPT plus exposure)

- mononuclear infiltrat
- epitheloid cells
- giant cells
- granuloma

Schreiber et al. 1999
Intracutaneous Beryllium Test

Histological characteristics of macroscopically positive tests in 10 patients with CBD (positive BeLPT plus exposure)

- mononuclear infiltrat
- epitheloid cells
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2 at day 28, 1 at day 56, and 1 at day 64

Schreiber et al. 1999

35.36
Problems in Beryllium Skin Testing

- discrimination between specific and unspecific reactions
- time point of biopsy
- sensitization

need for an easy test
LASER Microprobe Mass Spectrometry

Entzian P et al, 1998
LASER Microprobe Mass Spectrometry

Entzian P et al, 1998
LASER Microprobe Mass Spectrometry

Entzian P et al, 1998
LASER Microprobe Mass Spectrometry

Entzian P et al, 1998
Beryllium in Lung Tissue
Flameless Atomic Absorption Spectrophotometry

Control (n = 70) 3.3

Sarcoidosis (n = 2) 8

Coal miners (n = 26) 600

CBD cases (n = 66) 0.6 - 2.0

1 10 100 1000 10000 100000
ng Beryllium per gram tissue

adapted from Verma DK et al, 2003
BrdU-ELISA

Wemme et al, 1992
Pipetting Protocol for BeLPT
Estimating Proliferation by BrdU-ELISA

- blank, MNCs only
- control, MNCs plus BrdU
- positive control, ConA
- positive control, PHA

BeSO₄ 10⁻⁵ – 10⁻¹⁰ mol / L
Beryllium-Lymphocyte Proliferation Test (BeLPT)

mononuclear cells

- cell culture + Beryllium
- BrdU-incorporation

ELISA

stimulation index (SI)

Spont. Prolif PHA

ConA 10^{-5} 10^{-6} 10^{-7} 10^{-8} 10^{-9} 10^{-10}

BeSO_4
Beryllium-Lymphocyte Proliferation Test (BeLPT)

mononuclear cells

| cell culture + Beryllium
| BrdU-incorporation

ELISA

stimulation index (SI)

1st test

2nd test

100

10

1

Spont. Prolif PHA ConA 10^{-5} 10^{-6} 10^{-7} 10^{-8} 10^{-9} 10^{-10} BeSO_4
Beryllium-Lymphocyte Proliferation Test

BeLT (positive / negative)

- Berylliosis +
- Berylliosis -
- Exposed +
- Exposed -
- Controls +
- Controls -
- Sarcoidosis +
- Sarcoidosis -
- Tuberculosis +
- Tuberculosis -

BeLT positive
BeLT negative
Prednisolone BeLT negative

Schreiber et al. 1999
### Results of BeLPT in Beryllium Exposed and Unexposed Individuals

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>n</th>
<th>total</th>
<th>Exp.</th>
<th>BeLPT</th>
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<tbody>
<tr>
<td>CBD</td>
<td>21</td>
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<td>29</td>
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<tr>
<td>Healthy ns</td>
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<tr>
<td>Healthy s + exp</td>
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<tr>
<td>Sarcoid. exp</td>
<td>35</td>
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<tr>
<td>Healthy exp, ns</td>
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Müller-Quernheim J et al, submitted
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</table>

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## Occupational Settings with Beryllium Exposure Identified by Occupational Case History

<table>
<thead>
<tr>
<th>Occupational Beryllium Exposure</th>
<th>CBD</th>
<th>Exp Sens Healthy</th>
<th>Exp NS Healthy</th>
<th>Sarcoidosis exposed</th>
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</thead>
<tbody>
<tr>
<td>Dental technician, dentist</td>
<td>13</td>
<td>1</td>
<td>4</td>
<td>10</td>
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<tr>
<td>Engine develop., mechanics, automobile industry</td>
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<td>2</td>
<td>1</td>
<td>7</td>
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<td>Brass alloys, Be-alloys, stainless steel</td>
<td>3</td>
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<td>14</td>
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<tr>
<td>Metallurgic factory</td>
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<td>4</td>
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<tr>
<td>Aircraft production and maintenance</td>
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<td></td>
<td>2</td>
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<tr>
<td>Non-sparking tools</td>
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<td></td>
<td>1</td>
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</tr>
<tr>
<td>Radiation shielding</td>
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<td>1</td>
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<tr>
<td>Military vehicle armour</td>
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<tr>
<td>Fluorescent lamps</td>
<td>2</td>
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<tr>
<td>Microelectronics, electrical relays</td>
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<td>Chemical industry (catalysts, glass additives etc)</td>
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<tr>
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<tr>
<td>Ore mining</td>
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<tr>
<td>Grinding of optical lenses / precision instruments</td>
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<tr>
<td>Indirect (contaminated garments)</td>
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Conclusions

- Chronic Beryllium Disease can be found in cohorts diagnosed as sarcoidosis.
- Occupational exposure can be identified in a wide spectrum of industries and trades.
- This study gives evidence that CBD is underdiagnosed in industrialized nations.
- Occupational screening should be considered.
- Other tests cannot substitute for BeLPT.
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