ESTIMATING THE PREVALENCE OF CLINICAL MANGANISM FROM A CASCADED SCREENING PROCESS IN A SOUTH AFRICAN FERROMANGANESE SMELTER

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Occurrence of clinical manganism

• focuses entirely on clinical manganese toxicity

• Reports since 1837 (Couper)

• Reports are:
  – occupational
  – non occupational
    • chronic hepatic failure
    • Intravenous drug abuse
• **Study designs**
  – early case reports and case series
  – a few early mass screenings of populations at risk
  – a few more recent nonoccupational case series
  – Even fewer occupational epidemiological studies
  – Specifically using modern diagnostic methods
  – Most modern studies examine subclinical neurotoxicity

• **Diagnosis of clinical manganism appears recursive**
  – few cases
  – reports echo previous reports

• **Clinical picture is parkinsonism plus neuropsychiatric abnormalities**
Occurrence of clinical cases: ACGIH/IEH

- Remarkably few cases in last 200 years (other than in welders)
  - <500
  - with about 12 since the 1980s

- Reported cases arise typically @ very high exposures >> 5mg/m³ total dust
  - ACGIH TLV from 1982 – 1995 was 5mg/m³
  - IEH in 2003 reported no cases < 5mg/m³
Of recent note

• an emergent epidemic of clinical manganism claims in welders.

• welders studies using modern diagnostic criteria (eg UPDRSIII) – Racette 2006 (found between 6 and 13% prevalence of parkinsonism in 2081 medico-legal referrals)

• clinical and neuropathological reviews of manganism in relation to IPD – Olanow 2007, Jankovic 2006

• The large number of medico-legal referrals in welders seems out of proportion to the rarity of clinical manganism cases in the rest of the manganese industry
Background to study

- TV exposure of cases from a ferromanganese smelter
- Study smelter decided to institute a surveillance system
Methods

- cross-sectional cascaded screening 2006/7
- 754 smelter employees screened - 744 fully, 10 partially
- 3 levels of screening
- Other investigations MRI, MnB, Fe studies and Liver function tests where indicated.
Level 1 screening

- All 754 smelter employees in 2006/7
- by an occupational health nurse
- using 9 questions and
- 9 brief neurological examination procedures.
- referral if > 1 symptom
  or >=1 neurological sign
  or MnB > 40 μg/l
Level 2 screening

- a full neurological examination by an occupational medical practitioner
- Referral if any abnormal findings
Level 3 screening

• a movement disorders super-specialist neurologist and

• a specialised neuropsychologist.
Level 3 screening: neurological diagnosis

• UPDRSIII threshold $\geq 10$ (range = 0 – 108)
• $\geq 2$ of the **cardinal signs** of parkinsonism present Bradykinesia, Tremor, Rigidity, Postural instability / gait
• **Qualitative** clinical evaluation of **pattern and authenticity** of cardinal signs wrt a diagnosis of parkinsonism
• Impact of **modifying factors**
• Consistency with **characteristics reported for Mn induced parkinsonian**
Level 3 screening: Neuropsychological Diagnosis

- questionnaire measuring **affective and other symptoms**

- **11 tests with mostly SA norms**
  - **Cognitive domains**
    - attention
    - Concentration
    - Memory
    - Language
    - Construction
    - Executive functions

- **Fine motor function**
3 step diagnostic algorithm
Step 1: Neurological diagnosis of parkinsonism

<table>
<thead>
<tr>
<th>Neurological diagnosis</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neurologic signs</td>
<td>Normal</td>
</tr>
<tr>
<td>Other identifiable condition is responsible for the clinical neurological presentation.</td>
<td>Other condition</td>
</tr>
<tr>
<td>Some features of parkinsonism are present which are not explained by any other condition.</td>
<td>*Possible</td>
</tr>
<tr>
<td>Parkinsonism present</td>
<td>*Definite</td>
</tr>
</tbody>
</table>

* It is possible to have another condition and still be classified with possible or definite parkinsonism after taking into account the impact of that other condition on the clinical presentation.
Step 2: Assessment of Neuropsychological Abnormality

<table>
<thead>
<tr>
<th>Neuropsychological Findings</th>
<th>Classification for findings consistent with manganism</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (affective and behavioural) symptoms</td>
<td>Normal</td>
</tr>
<tr>
<td>All cognitive tests normal</td>
<td></td>
</tr>
<tr>
<td>Other confirmed condition present explains all</td>
<td>Other</td>
</tr>
<tr>
<td>Symptoms present.</td>
<td>Possible</td>
</tr>
<tr>
<td>Within any given cognitive domain* some test results are abnormal and others normal. May be explained by manganism or other condition.</td>
<td>Probable</td>
</tr>
<tr>
<td>Symptoms present.</td>
<td></td>
</tr>
<tr>
<td>Within any given cognitive domain all results are abnormal; in other cognitive domains results may be normal or a combination of normal and abnormal. Difficult to account for by reference to other condition.</td>
<td></td>
</tr>
</tbody>
</table>

* “Cognitive domain” refers to a broad area of cognition. Major domains include attention and concentration; memory; language; construction; and executive functions.
Step 3: Embellishment of results

- A problem generally in this difficult/contested area
- If suspected then taken into account when classifying
- Not specifically included in classification system
- Classification is rather made on the basis of clinical judgement
Step 4: Diagnosis of clinical manganism

- Neurological diagnosis of **possible or definite parkinsonism** is a pre-requisite.

- Neuropsychological assessment of **possible or probable abnormality** tends to support a neurological diagnosis of possible or definite clinical parkinsonism as manganism.

- **Embellishment or inconsistency** of symptoms and neuropsychological test scores supports a neurological classification of normal or other condition & undermines a possible or definite clinical manganism classification.

- **Substantial cumulative manganese exposure** (high intensity and long duration) required.
Sensitivity analysis

• **OH Service problems** and **diagnostic uncertainty** about manganism before the full diagnostic algorithm was developed

• resulted in **10 referrals** who were **certified manganism** cases by the state compensation authorities.

• They were only assessed up to Level 2 in the screening programme, and

• Were never examined by the study specialists.

• The 10 were both included and excluded from the analyses of results
Results
Exposure context - environmental

- Total manganese dust was **mostly within** (<5mg/m$^3$) or **near** (< 7 mg/m$^3$) the SA OEL, with highest and isolated outlier at 24 mg/m$^3$.

- Consequently it is probable that there have been long term exposures near and above 5 mg/m$^3$, but only in a few jobs.
Exposure context – biologic exposures

Mean 15.6 (SD=11.9) Range 2.7 - 117.5

Median 12.8  IQR  3.4 – 86.2
Screening results

- Of **744** employees screened with the full diagnostic algorithm:
  - @ Level 1 the nurse referred **152 (20.3%)**
  - @ Level 2, the doctor referred **27 (3.5%)**
  - @ Level 3, the specialists found

- No definite manganism cases, while **1 (0.13%)** employee was found to have possible manganism.

- A sensitivity analysis assuming that all 10 compensated cases were either normal, or alternatively had definite manganism, yielded a prevalence range for definite manganism from **0% to 1.3%**.
Level 3 screening: neurological diagnosis  \( n = 27 \)

- **UPDRSIII** threshold \( \geq 10 \) \((\text{range} = 0 – 108)\) 14 or 9 > 10
- \( \geq 2 \) of the **cardinal signs** of parkinsonism present Bradykinesia, Tremor, Rigidity, Postural instability / gait
- **Qualitative** clinical evaluation
  - **Pattern and authenticity** of cardinal signs wrt a diagnosis of parkinsonism
    - high bradykinesia score but absence of rigidity
    - Mild signs seen in normal people eg tone increase with failed relaxation
    - Bizarre features e.g. psychogenic tremor, anticipatory response
    - Atypical features e.g. antalgic or hemiplegic gait.
- Presence of **modifying factors** impacting on the UPDRSIII score e.g. alcoholism, neuropathy, arthritis, \( \text{n max} = 1 \) poss,
- Features **characteristic of Mn induced parkinsonian** e.g.symmetrical, axial syndrome with emphasis on speech and gait, dystonia \( \text{none} \)
Discussion

- **10 compensated employees** were the first not the worst
- Not examined by the study specialist team
- Their medical records deemed *clinically similar* to the 27 employees examined by specialist team
- Accounting for *downward bias* when excluding the 10, true prevalence of definite manganism was likely to be either zero or close to zero.
• **no substantive clinical manganism problem** in this workforce or the previous smelter

• **no subclinical manganese effects** were found at the previous similar smelter

• **smelter exposures >> 0.2 mg/m³ (ACGIH)** and most likely have exceeded the national OEL of 5 mg/m³ for prolonged periods, but not by much and not for many

• borne out by **fairly high levels of MnB** in currently exposed

• However, apart from isolated outliers, exposures are at levels at which the ACGIH and IEH reviews lead us to **expect an absence of clinical manganism**

• **So our main finding is not that mysterious**
Comparing recent UPDRSIII means and ranges

<table>
<thead>
<tr>
<th>Study</th>
<th>UPDRS score</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swiss liver failure</td>
<td>38 (20-61)</td>
<td>UPDRSIII</td>
</tr>
<tr>
<td>Ukrainian series</td>
<td>50(26-73)</td>
<td>Total UPDRS</td>
</tr>
<tr>
<td>Ukrainian series</td>
<td>?30(-)</td>
<td>UPDRSIII</td>
</tr>
<tr>
<td>Latvian qat addicts</td>
<td>40(22-59)</td>
<td>Total UPDRS</td>
</tr>
<tr>
<td>Latvian qat addicts</td>
<td>20.7 (8-34)</td>
<td>UPDRSIII</td>
</tr>
<tr>
<td><strong>Our 27 smelter workers @ level 3</strong></td>
<td><strong>9.4 (0-24)</strong></td>
<td><strong>UPDRSIII</strong></td>
</tr>
<tr>
<td><strong>conservatively</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bowler (2007) welders</strong></td>
<td><strong>6.6</strong></td>
<td><strong>UPDRSIII</strong></td>
</tr>
</tbody>
</table>
## Comparing MnB values

<table>
<thead>
<tr>
<th>Study</th>
<th>MnB mean (Range)</th>
<th>Current Exposure</th>
<th>Cases Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swiss liver failure</td>
<td>23 (8-54)</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Latvian qat addicts</td>
<td>45 (11-116)</td>
<td>yes current users</td>
<td>yes</td>
</tr>
<tr>
<td>Latvian qat addicts</td>
<td>19 (6-40)</td>
<td>no ex-users</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Study smelter workers</strong></td>
<td><strong>15.6 (3-118)</strong></td>
<td>yes</td>
<td>? 1 possible</td>
</tr>
<tr>
<td>Our previous smelter study</td>
<td>11.7(3-44)</td>
<td>yes</td>
<td>Not measured</td>
</tr>
<tr>
<td>Our previous controls</td>
<td>6.2 (3-11)</td>
<td>no</td>
<td>Not measured</td>
</tr>
<tr>
<td>Mn Mineworkers</td>
<td>8.5 (2-24)</td>
<td>yes</td>
<td>Not measured</td>
</tr>
<tr>
<td>Russian welders</td>
<td>8.6 (4-24)</td>
<td>yes</td>
<td>Not measured</td>
</tr>
<tr>
<td>Russian controls</td>
<td>6.9 (3-14)</td>
<td>no</td>
<td>Not measured</td>
</tr>
</tbody>
</table>
A question: Why don’t we see manganism in individual smelter workers with similar MnB levels to liver failure cases and IV drug abusers?

- Of 686 smelter workers who had MnB taken while currently exposed
  - 64% of smelter workers with MnB > 12
  - 27% of smelter workers with MnB > 20
  - 12% of smelter workers with MnB > 40
Remaining mysteries

• Why did we not find subclinical neurotoxicity at similar exposure levels in our previous smelter study?

• Why do welders with environmental (respirable dust) exposures twice as high, have much lower blood Mn levels than our previous and current smelter workers? Are ultrafine particles mainly not absorbed?

• Why do such welders have subclinical neurotoxicity (Ellingsen)?

• Why such an epidemic of cases of clinical manganism in welders?

• Do Mn nanoparticles exert different effects at similar MnB levels? Eg olfactory transport?

• Is the approach to clinical diagnosis of manganism (in welders) consistent?

• Or are we dealing with a medico-legal construct?
• Does manganese-induced parkinsonism or clinical manganism really exist as an occupational disease at today’s workplace exposures?

• Does occupational or environmental Mn exposure aggravate IPD?

• Given the extreme rarity of IPD in Black African workers, can we expect different findings in South Africa also for manganism to elsewhere?