

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 $\mu\text{g/l}$

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 ≥ 10 (range = 0 – 108)
- ≥ 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

Neurological diagnosis	Classification
No neurologic signs	Normal
Other identifiable condition is responsible for the clinical neurological presentation.	Other condition
Some features of parkinsonism are present which are not explained by any other condition.	*Possible
Parkinsonism present	*Definite

* 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

Neuropsychological Findings	Classification for findings consistent with mania
No (affective and behavioural) symptoms All cognitive tests normal	Normal
Other confirmed condition present explains all	Other
Symptoms present. Within any given cognitive domain* some test results are abnormal and others normal. May be explained by mania or other condition.	Possible
Symptoms present. 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.	Probable
* “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 ($<5\text{mg}/\text{m}^3$) or near ($< 7 \text{ mg}/\text{m}^3$) the SA OEL**, with highest and isolated outlier at $24 \text{ mg}/\text{m}^3$.
- Consequently it is probable that there have been long term exposures near and above $5 \text{ mg}/\text{m}^3$, 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 ≥ 10 (range = 0 – 108) **14 or 9 > 10**
- ≥ 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, . **n max = 1 poss,**
- Features **characteristic of Mn induced parkinsonian**
e.g. symmetrical, axial syndrome with emphasis on speech and gait, dystonia **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 manganese problem** in this workforce or the previous smelter
- **no subclinical manganese effects** were found at the previous similar smelter
- smelter **exposures** \gg 0.2 mg/m^3 , (ACGIH) and most likely have exceeded the national OEL of 5 mg/m^3 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 manganese**
- **So our main finding is not that mysterious**

Comparing recent UPDRSIII means and ranges

Study	UPDRS score	Scale
Swiss liver failure	38 (20-61)	UPDRSIII
Ukrainian series	50(26-73)	Total UPDRS
Ukrainian series	?30(-)	UPDRSIII
Latvian qat addicts	40(22-59)	Total UPDRS
Latvian qat addicts	20.7 (8-34)	UPDRSIII
Our 27 smelter workers @ level 3	9.4 (0-24) - conservatively	UPDRSIII
Bowler (2007) welders	6.6	UPDRSIII

Comparing MnB values

Study	MnB mean (Range)	Current Exposure	Cases Present
Swiss liver failure	23 (8-54)	yes	yes
Latvian qat addicts	45 (11-116)	yes current users	yes
Latvian qat addicts	19 (6-40)	no ex-users	yes
Study smelter workers	15.6 (3-118)	yes	? 1 possible
Our previous smelter study	11.7(3-44)	yes	Not measured
Our previous controls	6.2 (3-11)	no	Not measured
Mn Mineworkers	8.5 (2-24)	yes	Not measured
Russian welders	8.6 (4-24)	yes	Not measured
Russian controls	6.9 (3-14)	no	Not measured

A question: Why don't we see manganese 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?