Barking, Havering and Redbridge University Hospitals NHS Trust

An unexpected cause of neurological deterioration

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Background

- 70 year old female
- History of iron deficiency anaemia, bipolar disorder, Type 2 diabetes, hypertension and hypothyroidism
- On a range of medications including metformin, simvastatin, amlodipine, sertraline, levothyroxine, omeprazole, zopiclone, promethazine.

Presentation

- Presented to A&E with confusion and slurred speech
- Admitted under Neurology
- Further investigation uncovered an 18 month history of cognitive impairment, involuntary movement, personality change, slurred speech, unsteady gait and frequent headaches with deterioration noted in the two weeks prior to admission alongside an increase in promethazine use.

Investigations

A series of investigations were performed as an inpatient including:

Imaging

- MRI Brain: symmetrical T1 hyperintensive signal change
  - This can be caused by methaemoglobin, melanin, lipid, protein, calcium, iron, copper, or manganese deposition
- Liver imaging: cirrhotic liver with fatty infiltration and mild splenomegaly

Blood results

- U&E and calcium results were within reference intervals. Other results included:

Blood results 29/06					
Total bilirubin	9 umol/L	(1 – 21)	Haemoglobin	**100** g/L	(115 – 155)
ALP	119 IU/L	(30 – 130)	CarboxyHb	1.9%	(<2)
Total protein	73 g/L	(60 – 80)	Caeruloplasmin	0.27 g/L	(0.16 - 0.45)
Albumin	**34** g/L	(35 – 50)	Copper	**21.9** umol/L	(11 – 20)
Globulin	**39** g/L	(18 – 36)	Zinc	**8.5** umol/L	(11 – 24)
ALT	12 IU/L	(<33)	Blood manganese	**654.46** nmol/L	(72.8 – 218.5)
Iron	6 umol/L	(5.8 - 34.8)	Ammonia	**97.7** umol/L	(11 – 50)

CSF results

A range of CSF investigations were conducted with markers of neurodegeneration (Tau, A-Beta 1-42) within reference range, negative results for markers of CJD, and CSF oligoclonal band analysis indicating a systemic inflammatory response.

Repeat blood results

The raised manganese result was confirmed on a repeat sample. To reduce the risk of contamination, clinicians were advised to collect the sample in a trace element free sodium heparin tube using a plastic cannula, or to discard the first blood draw if using a stainless steel needle.

Blood results 05/07		
Blood manganese	**595.65** nmol/L	(72.8 – 218.5)

Diagnosis

Several causes of manganese toxicity were considered:

- **Contaminated sample**: Blood tubes and stainless steel blood collection needles may be contaminated with manganese; contamination excluded following repeat sample
- **Occupational exposure**: common cause but considered not appropriate for this patient based on her history
- **Environmental exposure**: manganese can be found in fuel additives, pesticides, contaminated water, medical contrast agents, and nutritional sources; considered unlikely source of manganese for this patient as there was no obvious exposure and she was not taking any nutritional supplements
- **Genetics:** inherited manganese transporter disorders considered unlikely as there was no family history and manganese levels expected to be higher
- **Cirrhosis:** manganese toxicity may be caused by accumulation due to cirrhosis and was considered the likely cause in this patient.

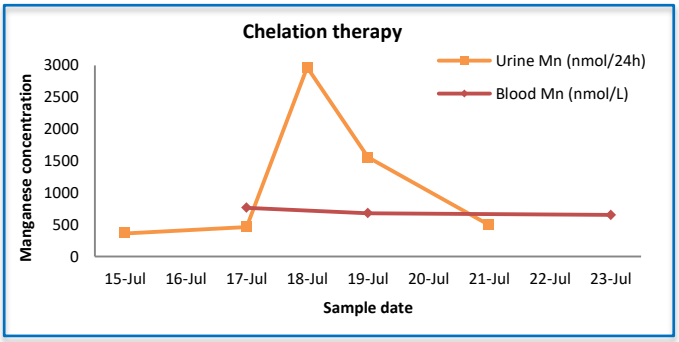
The patient was diagnosed with **acquired hepatocerebral degeneration due to cerebral manganese accumulation secondary to liver cirrhosis**. Acute on chronic deterioration was considered possible due to the increased promethazine use prior to admission.

Treatment

Following advice from TOXBASE®, standard chelation therapy was commenced:

- Sodium calcium edetate 75 mg/kg once daily by IV infusion over 1-2 hours for 5 days
- Continuous 24 hour urine collection for manganese analysis
- Daily blood samples for manganese, zinc, U&E and LFT
- Clinical impact reviewed after three days to decide whether to continue chelation
- Zinc supplementation given alongside chelation therapy to reduce the risk of zinc depletion.

Urine and blood manganese levels are shown in the graph below. Chelation therapy showed a decrease in blood manganese concentrations and an increase in urine manganese. An improvement in symptoms was described, although considered to be due to multifactorial changes, and the patient was discharged a week later.

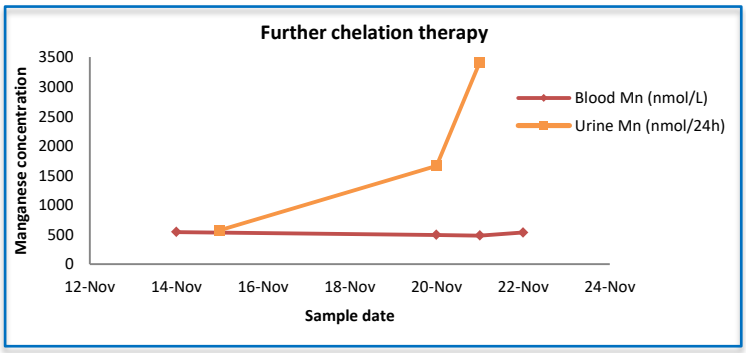


Follow Up

Neurology outpatient review seven weeks after discharge showed blood manganese levels had almost halved from initial levels but a slow deterioration in neurological symptoms continued and further chelation therapy was recommended.

Blood results 13/09		
Blood manganese	**371** nmol/L	(72.8 – 218.5)

Sodium calcium edetate was administered with zinc supplementation for 3 days and urine and blood manganese levels monitored. Urine manganese levels increased but there was no decrease in blood manganese (graph below) and no subsequent improvement in cognitive state.



Further Follow Up

- The patient was regularly monitored by the Neurology and Hepatology teams.
- Blood manganese levels continued to be raised; six months after the second chelation therapy, blood manganese was 746 nmol/L
- There was considered no role for further chelation therapy
- Hepatology assessment showed hepatic encephalopathy but no features of decompensation
- Marked deterioration in neurological symptoms was noted over the next 9 months
- Sadly the patient passed away

Learning Outcomes

This case highlights several learning points:

- Manganese toxicity should be considered as a cause of neurological deterioration if changes seen on imaging are suggestive even if there is no obvious source of manganese
- The importance of liaison between the laboratory and clinical teams to ensure appropriate samples are collected for unusual tests and that these are processed within a relevant timeframe
- The use of discussion with Specialist Toxicology laboratory regarding collection of appropriate samples to reduce risk of contamination and interpretation of results
- The value of TOXBASE® and the National Poisons Information Service for advice on investigation and treatment of toxicity cases for both clinicians and the laboratory

Acknowledgements

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