



## Neurology in metal-on-metal hip arthroplasty a case of suspected prosthetic hip-associated cobalt toxicity

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**Metal-on-Metal hip arthroplasty was a frequently performed procedure, until concerns raised. Metal ion concentrations raise after the placement of a MoM prosthesis. This might lead to toxic concentrations of cobalt ions which might result in cardiotoxicity, thyroid toxicity and/or neuro-ocular toxicity. It is possible that raised cobalt and chromium concentrations have a role in the development of neurodegenerative diseases like Creutzfeldt-Jakob. We describe a patient with a MoM prosthesis who developed neurological symptoms were we thought of cobalt intoxication but turned out to be Creutzfeldt-Jakob disease.**

**Keywords** : Metal-on-Metal hip arthroplasty ; hip resurfacing ; cobalt intoxication ; cobaltism ; PHACT ; neurodegenerative disease ; Creutzfeldt-Jakob disease.

### INTRODUCTION

In the early 90s, metal-on-metal (MoM) hip replacement became a worldwide accepted procedure. It was thought that the articulation of two metal surfaces, using an alloy consisting of cobalt, chromium and molybdenum, would produce less volumetric wear debris (11). Although, since the recent years concerns were raised because of high failure rates. Adverse reactions to metal

debris (ARMD) are frequently seen and metal ion concentrations of cobalt and chromium, raise significant after the placement of a resurfacing prosthesis (9)(10). Several cases of cobalt intoxication due to metal-on-metal prosthesis have been published. We describe a case of suspected cobalt intoxication after the placement of a MoM hip resurfacing prosthesis.

### CASE REPORT

A 55-year old women underwent unilateral hip resurfacing because of symptomatic coxarthrosis in July 2007. The patient was followed up yearly without any complaints. According to the Dutch protocol, MR-imaging and blood ion metal concentrations (Table I) were performed. In spring

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*Conflict of interest: All authors declare that they have not received any funding or other benefits in support of this study. No relevant financial relationships to disclose.*

Table I. — Chronological Cobalt Concentrations

Date	Chromium ug/L	Cobalt in µg/L
02-11-2012	30.8	49.1
02-01-2014	22.4	27.3
17-11-2014*	11.6	10.0
12-2014 MoM Revision Surgery		
23-12-2014	7.2	3.3
11-03-2015	4.1	3.0

\* measurement was not known before revision

\*\* Cobalt: To convert from µg/L to nmol/L – multiply by 16.97

\*\*\* Chromium: To convert µg/L to nmol/L – multiply by 19.20

of 2014 patient started to experience amnesia and diplopia. The patient was analysed by the neurology department. MR-imaging of the brain and blood tests (thyroid-stimulating hormone, calcium, vitamin B12, folic acid) showed no abnormalities. She returned in the autumn of 2014 with progressive complaints and new onset ataxia and dysarthria. The patient was admitted and immunoglobulin therapy was started, with auto-immune encephalitis as working diagnosis. Normal serum homocysteine and vitamin E were found. Immunological testing showed no paraneoplastic anti-neuronal antibodies and antibody tests for myasthenia gravis, Lambert-Eaton Myastenic Syndrome and encephalitis were all negative. Electromyography (EMG) and electroencephalography (EEG) showed no abnormalities. A liquor puncture showed a normal IgG-index, was negative for borrelia, syphilis, neurotropic viruses and normal S100, 14-3-3, NSE, Tau, fosfo-Tau and amyloid-B42. A PET-CT showed no signs of malignancy. After five days of immunoglobulin therapy no improvement was objectified. After multidisciplinary consultation we chose for revision of the resurfacing prosthesis because of suspected cobalt intoxication and lack of another diagnosis. Chelation was considered insufficiently effective. A revision was performed with a cemented acetabular component and a cemented stem with a metal-on-polyethylene bearing surface. Hereafter the metal ion concentrations dropped to slightly elevated levels (Table I). The patient recovered well from the surgery without complications, but the neurological complaints

persisted. The patient showed a progressive dysarthria, dysphasia and dysphagia. She became wheelchair-bound and presented with a new trunk ataxia, dystonia and tremor capitis. Multidisciplinary consultation with a tertiary centre led to a diagnosis of a fast-cerebellar progressive supranuclear palsy (PSP)-variant, possibly Creutzfeldt-Jakob disease (CJD). No additional tests were performed, because of the clinical condition of the patient. She passed away in November 2015. Brain obduction showed an atypical type of Creutzfeldt-Jakob disease, based on a mutation on codon D178N at the MV2 protein.

## DISCUSSION

We describe a patient with suspected cobalt intoxication due to a MoM prosthesis on which we performed revision surgery. The release of chromium ions was initially reported as non-hazardous because of its trivalent (III) form (8). Although, the Medicines and Healthcare Products Regulatory Agency (MHRA) reported that long-term consequences of increased chromium ion levels is not well known (4). This is in contrast to the release of cobalt ions which might lead to systemic complaints known as 'Prosthetic Hip-Associated Cobalt Toxicity' (PHACT) (5).

The laboratory results of our patient show a linear decline since the first measurement in 2012, at 5-years postoperatively. It is possible that metal ion concentrations were even higher in the first years after surgery, because metal ion concentrations rise significantly after the placement of a MoM prosthesis (1,9,10). The decline over time is consistent with van der Straeten et al. who reported a decrease of metal ion concentrations in patients with a well-functioning unilateral BHR (Smith & Nephew) after more than ten years postoperatively (16). Also Savarino et al. reported that cobalt concentrations have a tendency to decrease over time, especially in females with BHR (14). In contrast, Galea et al. found a minor increase in cobalt concentrations between early and mid-term follow-up in patients with a ASR Hip Resurfacing (Depuy) (6).

Three main categories of cobalt toxicity can be distinguish: cardiotoxicity, thyroid toxicity

and neuro-ocular toxicity. Neuro-ocular toxicity is reported most common and manifest as visual impairment, sensorineural hearing loss, cognitive decline and peripheral neuropathy. Zywiell et al. reported neuro-ocular toxicity in 13 of 18 patients, Bradberry et al. in 14 of 18 patients. Gessner et al. reviewed 25 intoxications and reported audiovestibular in 52%, peripheral motor sensory in 48% and optic and psychosocial symptoms in 32%. Polycythemia, nausea, anorexia and unexplained weight loss have also been described. (2,7,17) Neuro-ocular toxicity is often accompanied by cardio- or thyroidtoxicity (Table II).

Table II. — Percentage of Reported Types of Toxicity

	Bradberry et al. (n=18)	Gessner et al. (n=25)	Zywiell et al. (n=18)
Cardiotoxicity	61%	60%	56%
Thyroidtoxicity	50%	48%	50%
Neuro-oculartoxicity	78%	52%	72%

Literature search showed that 34 articles have been published in recent years describing 26 cases of cobalt intoxication, without counting the cases of metal allergy (2,7,17). Most cases describe an intoxication after revision of a ceramic-on-ceramic (CoC) prosthesis to a metal-on-polyethylene (MoP). Only 12 patients have been reported with cobalt intoxication after the primary placement of a MoM. Mean follow-up from original implantation or revision to presentation is 44 months [9 – 99]. Hip symptoms are common (84%) (7). Current literature is still inconclusive over the height of cobalt concentrations before toxicity might occur (4). The European Scientific Committee (SCENHIR) focused on the safety of MoM joint replacements and determined the threshold for clinical concern at 7  $\mu\text{g/L}$  (15). Paustenbach et al. did a literature research and concluded that significant systemic complaints of cobaltism most likely will not occur when concentrations of cobalt ions stay below 300  $\mu\text{g/L}$  (12). But, there is a clear difference in the serum cobalt concentrations found in patients with cobalt intoxication after revision of a CoC and those with a primary MoM. The 9 CoC patients

found by Gessner et al. showed a mean serum cobalt concentration of 613  $\mu\text{g/L}$  [398–1085], while Bradberry et al. reported a median of 506  $\mu\text{g/L}$  [353 – 6521] in 10 patients. For patients with a primary MoM a mean cobalt concentration of 104  $\mu\text{g/L}$  [10 – 398] was found by Gessner et al. in 16 patients. Bradberry reported a median concentration of 34.5  $\mu\text{g/L}$  [13.6 - 398.6] in 8 and Zywiell et al. reported a median serum concentration of 35  $\mu\text{g/L}$  [14 – 288] in their 8 patients (2,7,17). Seventeen percent showed concentrations less than 20  $\mu\text{g/L}$  and almost 50% less than 100  $\mu\text{g/L}$  (7).

There is little evidence for the use of chelation in cobalt intoxication. Although cobalt ion concentrations might reduce after therapy with chelating agents, the clinical effect is questionable. Definitive treatment is obtained with revision of the prosthesis and thereby eliminating the source (17). Full recovery is seen in almost all intoxicated patients, except for optic and audiovestibular symptoms (2). Unfortunately, the clinical condition of our patient did not improve after the revision. We believe that all neurological symptoms are attributed to the CJD. Especially because the MoM hip was asymptomatic, the metal ion concentrations declined over the years and the patient only showed neuro-ocular toxicity without cardio- and thyroid toxicity. Also, atypical CJD might have a longer duration than the typical form (13). Excessive amounts of metal ions result in neurotoxicity and are associated with oxidative stress, mitochondrial dysfunction and protein misfolding. Synthesizing neurotransmitters and maintaining homeostasis is harder for the injured neurons. This and neurotoxicity might result in neuronal death, initiating a vicious cycle of toxicity (3). It seems possible that increased cobalt ion concentrations due to a MoM resurfacing prosthesis contribute to the development of a neurodegenerative disease like CJD.

## CONCLUSION

In a patient with a metal-on-metal hip prosthesis and neurological complaints one should always think of a possible cobalt intoxication. Although rare, a clinical well functioning MoM with cobalt ion concentrations <20  $\mu\text{g/L}$ , and possibly <7

µg/L, might also result in cobalt intoxication. Prosthetic Hip-Associated Cobalt Toxicity requires a multidisciplinary approach with collaboration between the departments of orthopaedic surgery, neurology, radiology and clinical chemistry to pick the right patients for revision surgery. Further research to the development of neurodegenerative diseases due to raised cobalt ion and chromium ion concentrations is necessary.

## REFERENCES

1. **Amstutz HC, Campbell PA, Dorey FJ et al.** Do ion concentrations after metal-on-metal hip resurfacing increase over time? A prospective study. *J Arthroplasty*, 2013 ; 28 : 695-700.
2. **Bradberry SM, Wilkinson JM, Ferner RE.** Systemic toxicity related to metal hip prostheses. *Clin Toxicol (Phila)*, 2014 ; 52 : 837-47.
3. **Chen P, Miah MR, Aschner M.** Metals and Neurodegeneration. *F1000 Res*, 2016 ; 5.
4. **Cohen D.** All patients with metal-on-metal hip implants should undergo tests, says MHRA. *BMJ*, 2017 ; 358 : j3246.
5. **Devlin JJ, Pomerleau AC, Brent J et al.** Clinical features, testing, and management of patients with suspected prosthetic hip-associated cobalt toxicity: a systematic review of cases. *J Med Toxicol*, 2013 ; 9 : 405-15.
6. **Galea VP, Laaksonen I, Matuszak SJ et al.** Mid-term changes in blood metal ion levels after Articular Surface Replacement arthroplasty of the hip. *Bone Joint J*, 2017 ; 99-B : 33-40.
7. **Gessner BD, Steck T, Woelber E, Tower SS.** A Systematic Review of Systemic Cobaltism After Wear or Corrosion of Chrome-Cobalt Hip Implants. *J Patient Saf*. 2019 Jun ; 15(2) : 97-104.
8. **Hart AJ, Quinn PD, Sampson B et al.** The chemical form of metallic debris in tissues surrounding metal-on-metal hips with unexplained failure. *Acta Biomater*; 2010 ; 6 : 4439-46.
9. **Langton DJ, Jameson SS, Joyce TJ et al.** Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: A consequence of excess wear. *J Bone Joint Surg Br*; 2010 ; 92 : 38-46.
10. **Langton DJ, Joyce TJ, Mangat N et al.** Reducing metal ion release following hip resurfacing arthroplasty. *Orthop Clin North Am*, 2011 ; 42 : 169-80.
11. **Maurer-Ertl W, Friesenbichler J, Sadoghi P et al.** Metal ion levels in large-diameter total hip and resurfacing hip arthroplasty-preliminary results of a prospective five year study after two years of follow-up. *BMC Musculoskelet Disord*, 2012 ; 13 : 56.
12. **Paustenbach DJ, Galbraith DA, Finley BL.** Interpreting cobalt blood concentrations in hip implant patients. *Clin Toxicol (Phila)*, 2014 ; 52 : 98-112.
13. **Poser S, Zerr I, Schroeter A et al.** Clinical and differential diagnosis of Creutzfeldt-Jakob disease. *Arch Virol Suppl*, 2000 ; 16 : 153-9.
14. **Savarino L, Cadossi M, Chiarello E et al.** How do metal ion levels change over time in hip resurfacing patients? A cohort study. *ScientificWorldJournal*, 2014; Article ID 291925 : 7 pages.
15. **SCENIHR** (Scientific Committee on Emerging and Newly Identified Health Risks). The safety of Metal-on-Metal joint replacements with a particular focus on hip implants. 25 September 2014.
16. **Van Der Straeten C, Van Quickenborne D, De Roest B et al.** Metal ion levels from well-functioning Birmingham Hip Resurfacings decline significantly at ten years. *Bone Joint J*, 2013 ; 95-B : 1332-8.
17. **Zywił MG, Cherian JJ, Banerjee S et al.** Systemic cobalt toxicity from total hip arthroplasties: review of a rare condition Part 2. measurement, risk factors, and step-wise approach to treatment. *Bone Joint J*, 2016 ; 98-B: 14-20.