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REVIEW ARTICLE

Clinical Features, Testing, and Management of Patients with Suspected Prosthetic Hip-Associated Cobalt Toxicity: a Systematic Review of Cases

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Abstract Safety concerns regarding cobalt-containing metal alloy hip prosthetics (Co-HP) have resulted in product recalls, a medical device alert, and issuance of guidance for clinicians. Recently, cases of suspected prosthetic hip-associated cobalt toxicity (PHACT) from Co-HP have been reported. Although little is known about suspected PHACT, these patients may be referred to medical toxicologists for evaluation and management recommendations. We searched MEDLINE, EMBASE, and unpublished abstracts from toxicology scientific meetings for references relevant to PHACT. Authors independently screened publications for inclusion criteria: publication in English, human study population, subject(s) are symptomatic (except for isolated hip pain), and cobalt values in any matrix (blood, serum, urine, CSF, synovial fluid) available for review. Data from 10 cases are reviewed. Patients with suspected PHACT had findings consistent with cobalt toxicity, including thyroid, cardiac, and neurologic dysfunction. Signs and symptoms appeared between 3 and 72 months after arthroplasty (median 19 months). Neurologic symptoms were most common. Ancillary testing varied considerably. All patients had elevated cobalt levels in one or more matrices. Enhanced elimination was attempted in 27 % of patients. At this time, the information currently available regarding patients with suspected PHACT is inadequate to guide clinical decision making. No consensus has been reached regarding the management of Co-HP patients with systemic symptoms. Indications for chelation have not been established and require further study. Improved case definitions, improved surveillance, and controlled studies are needed to elucidate the scope of this problem and guide future investigations.

Keywords Cobalt · Poisoning · Hip prosthesis · Arthroplasty · Cobalt toxicity

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Introduction

Hip replacement surgery using implantable metal components has been performed in North America for over 50 years. Recently, safety concerns—excessive revision rates, local reactions, and high metal ion levels—have resulted in product recalls, a medical device alert, and issuance of clinical guidance by the Food and Drug Administration (FDA) in the USA [1–4]. During the past 6 years, cases of systemic symptoms associated with cobalt-containing metal alloy hip prosthetics (Co-HP) have been reported [5–13]. A definitive causal link between Co-HP and systemic symptoms, as opposed to local reactions, has not been definitively established.

The FDA reports that 400,000 hip arthroplasty procedures are performed annually in the USA [4]. These procedures may involve total hip replacement (THR) or hip resurfacing. The

later involves the implantation of less prosthetic material. During THR, the articulating surfaces of the acetabulum and femoral head are replaced with prosthetic components consisting of ceramic-on-ceramic, metal-on-polyethylene, or metal-on-metal. All hip implant devices with metal components used in the USA contain cobalt alloys. However, the use of higher risk metal-on-metal hip devices in the USA is declining. Because most of these prosthetics were placed between 2003 and 2010, the prevalence of suspected prosthetic hip-associated cobalt toxicity (PHACT) may increase. Patients suffering from suspected PHACT may be referred to medical toxicologists for evaluation and management.

Our objective was to conduct a systematic review of suspected PHACT cases detailing the clinical features, laboratory evaluation, ancillary testing, and management of these patients. We hoped to provide guidance for medical toxicologists evaluating these patients.

Methods

On July 30, 2012, we electronically searched both MEDLINE and EMBASE. In order to maximize identification of relevant literature, we utilized a combination of index terms and free-text terms as has been previously recommended by the Cochrane Adverse Effects Methods Group [14]. MEDLINE search terms (medical subject headings and free-text) included "cobalt toxicity," "cobalt," "intoxication," "poisoning," "arthroprosthetic cobaltism," "hip prosthesis," "joint replacement," and "arthroplasty" while filtering by "case reports," "clinical trial," "comparative study," "controlled clinical trial," or "randomized controlled trial." The EMBASE search used similar terms (free-text and index) while filtering by "clinical trial," "randomized controlled trial," "controlled clinical trial," "multicenter study" and "article," "conference abstract," "conference paper," "journal," "letter," "note," or "report" for relevant abstracts. Two authors independently reviewed articles to determine if inclusion criteria were met. Any disagreement between reviewers was arbitrated by a third reviewer. We also manually reviewed abstracts presented at the 2011 North American Congress of Clinical Toxicology and the 10th Annual Congress of the Asia-Pacific Association of Medical Toxicology for unpublished cases meeting inclusion criteria. Additionally, the reference sections of included publications were searched for additional cases.

The following comprised our inclusion criteria: publication in English, study population includes human subject(s), cobalt levels in any matrix available for review, and patients having systemic symptoms. References that documented only localized joint symptoms did not meet the inclusion criteria and were excluded.

Results

Our search methods identified 60 references. Independent review of all identified references by two authors (JD, AP) resulted in complete agreement regarding publications meeting inclusion and exclusion criteria. The majority of references identified pertained to device failure, not suspected toxicity. Additional excluded references were animal studies, in vitro studies, letters, reviews, or reports published in languages other than English. No controlled studies were identified. Seven case reports and two case series were included, identifying 10 unique cases available for review.

Historical, laboratory, and ancillary testing features of the 10 patients are summarized in Table 1. Signs or symptoms appeared between 3 and 72 months after arthroplasty (median 19 months) and are listed by frequency of occurrence in Table 2. Hearing and cognitive impairment were the most frequently reported symptoms, occurring in at least half of the cases. Other commonly reported symptoms included paresthesias, visual impairment, headache, dysgeusia (metallic taste), dyspnea, rash or nail changes, fatigue, and weight loss. There was wide variation in the ancillary testing reported. Ancillary testing varied considerably and included nerve conduction studies, brain stem evoked potentials, audiometry, electromyography, brain magnetic resonance imaging, echocardiography, and pulmonary function testing. Table 3 summarizes the highest reported cobalt concentrations in different matrices for each case.

Discussion

Most of what is known about cobalt toxicity comes from cases of inhalation and ingestion of excess cobalt. The patients with suspected PHACT identified by our search have findings consistent with historic cobalt toxicity—thyroid, cardiac, and neurologic dysfunction. However, the lack of controlled comparison studies makes definitively linking these clinical features to elevated cobalt values problematic at this time.

Thyroid Dysfunction

Three cases of suspected PHACT were complicated by hypothyroidism. Pre-hip implant surgery thyroid function is not reported. These three patients were in their fifth decade of life; hypothyroidism is common at this age. However, thyroid dysfunction has been associated with cobalt toxicity [15]. Hypothyroidism was attributed to cobaltous chloride treatment for refractory anemia [16]. Further, occupationally exposed cobalt dye workers with low level chronic cobalt exposures had altered thyroid hormone metabolism despite the absence of clinical disease [17].

Table 1 Summary of suspected prosthetic hip-associated cobalt toxicity cases

Author/year	Patient age/ gender	Highest reported blood, plasma, or serum level	Latency to symptom onset	Prosthetic type	Major symptoms and physical findings	Ancillary test results
Steens et al. 2006	53/M	398 μg/L (serum)	24 months	"Metal head"	Neuro: hearing impairment, visual impairment, paresthesias, "toxic atrophy of the optical nerve and retinopathy with malfunction of the macula" Misc: dermatitis to head and neck	Audiometry testing post-revision surgery reported only and "revealed that his hearing was returning"
Oldenburg et al. 2009	55/M	625 μg/L (wb)	3 months	Aesculap NK 433K	Neuro: hearing impairment, poor concentration, cognitive decline, headaches, convulsions, paresthesias, decreased muscle mass, dysgeusia Cardio: tachycardia Misc: fatigue, >10 kg weight loss, nail discoloration, eczema, lingual film, hypothyroidism	NCT showed decreased conduction velocity and increased distal sensory latency of the peroneal nerve. Echocardiogram showed reduced systolic left ventricular function and concentric left ventricular hypertrophy. Myocardial biopsy showed interstitial fibrosis
Rizetti et al. 2009 and Pazzaglia et al. 2011[a]	58/F	549 μg/L (wb), 90 μg/L (plasma)	5 months	"Polyethylene liner coupled with cobalt–chromium head"	Neuro: severe hearing impairment, near total blindness, "mild distal sensory–motor disturbances," wheelchair bound due tolower limb hyposthenia Misc: hypothyroidism	EMG showed mild lower limb nerve amplitude reduction. Acoustic and visual evoked potentials showed bilateral absence of brainstem acoustic responses and irregular cortical visual responses. MRI brain showed hyperintensity of optic nerves and tracts
Ikeda et al. 2010	56/F	>400 μg/L (serum)	24 months	"Cobalt–chromium alloy head and a polyethylene liner"	Neuro: bilateral sensorineural hearing impairment, diminished deep tendon reflexes, painful dysesthesias and paresthesias, impaired joint position sense Misc: fever, malaise	NCT with no evoked sensory nerve action potential, but the results of motor conduction were normal. Audiometry testing showed hearing impairment. Sural nerve biopsy showed moderate axonal degeneration with no inflammatory changes in any sections
Tower 2010[b]	49/M	122 μg/L (serum)	3 months	DePuy ASR	Neuro: hearing impairment, visual impairment with optic nerve atrophy, anxiety, headaches, tinnitus, hand tremor, incoordination, cognitive decline Cardio: dyspnea Misc: fatigue, axillary rash, depression, irritability	Audiometry showed high-frequency hearing loss. Echocardiogram showed diastolic dysfunction. Imaging studies showed a large periprosthetic fluid collection. Skin patch testing showed no reactivity to cobalt
	49/M	23 μg/L (serum)	12 months	DePuy ASR	Neuro: hearing impairment, cognitive decline, vertigo Cardio: dyspnea Misc: rash	None reported
Mao et al. 2011	73/F	410 nmol/L (serum)[c]	53 months	DePuy ASR XL	Neuro: cognitive decline, memory difficulties, headaches, dysgeusia Misc: weight loss, anorexia, fatigue, depression	None reported

Table 1 (continued)

Author/year	Patient age/ gender	Highest reported blood, plasma, or serum level	Latency to symptom onset	Prosthetic type	Major symptoms and physical findings	Ancillary test results
	60/M	258 nmol/L (serum)[d]	36 months	DePuy ASR XL	Neuro: muscle cramps, cognitive decline, poor concentration Cardio: dyspnea, DOE Misc: lightheadedness, fatigue	None reported
Pelclova et al. 2011	56/M	506 μg/L (serum)	14 months	"Metal alloy containing cobalt, chromium, and titanium"	Neuro: hearing impairment, paresthesias, severe sensorimotor polyneuropathy of extremities with hypotonia and decreased muscle mass, diminished reflexes, difficulty walking Misc: weight loss (20 lbs.), subclinical hypothyroidism	Audiometry showed severe bilateral sensorineural hearing loss/deafness. Echocardiogram showed a large pericardial effusion and left ventricular hypertrophy. EMG showed no myogenic damage
Machado et al. 2012	75/M	230 nmol/L (plasma)[e]	~72 months	DePuy ASR	Cardio: dyspnea, exertional chest tightness, atrial fibrillation	Echocardiogram showed severely dilated left atrial and severe global systolic dysfunction. Myocardial perfusion imaging showed left ventricular ejection fraction of 21 %

DOE dyspnea on exertion, *EMG* electromyogram, *F* female, *M* male, *NCT* nerve conduction test, *wb* whole blood

[a] Both case reports about the same patient

[b] Same two patients are also described by Tower in "Cobalt Toxicity in Two Hip Replacements," State of Alaska Epidemiology Bulletin No 14, May 2010

[c] Reported reference range 0–20 nmol/L, equal to 24 μg/L

[d] Reported reference range 0–20 nmol/L, equal to 15 μg/L

[d] Reported reference range 0–20 nmol/L, equal to 13.6 μg/L

Table 2 Frequencies of reported signs, symptoms, and findings associated with suspected prosthetic hip-associated cobalt toxicity

Symptom or finding	Frequency
Neurologic	9/10
Hearing impairment	7/10
Cognitive/memory/concentration impairment	5/10
Paresthesias	5/10
Visual impairment	3/10
Headache	3/10
Dysgeusia/metallic taste	2/10
Optic nerve atrophy	2/10
Decreased muscle mass	2/10
Diminished reflexes	2/10
Difficulty walking	2/10
Tinnitus	1/10
Convulsions	1/10
Hypotonia	1/10
Hyposthenia	1/10
Joint proprioception impairment	1/10
Hand tremor	1/10
Incoordination	1/10
Vertigo	1/10
Muscle cramps	1/10
Cardiovascular	5/10
Dyspnea	4/10
Atrial fibrillation	1/10
Dyspnea on exertion	1/10
Tachycardia	1/10
Exertional chest tightness	1/10
Miscellaneous	9/10
Rash/dermatitis/nail findings	4/10
Fatigue	4/10
Weight loss	3/10
Hypothyroidism	3/10
Depression	2/10
Fever	1/10
Lingual film	1/10
Malaise	1/10
Irritability	1/10
Anorexia	1/10
Lightheadedness	1/10

Table 3 Highest reported cobalt concentrations measured in different matrices

Case report	Highest reported concentration
Steens et al. [5]	
Serum	398 μg/L
Cerebrospinal fluid	3.2 μg/L
Oldenburg et al. [6]	
Whole blood	625 μg/L
Urine, 24 h	16,500 μg/L
Synovial/pseudotumor	76 mg/L[a]
Rizetti et al. [7] and Pazzaglia et al. [11]	
Whole blood	549 μg/L
Plasma	90 μg/L
Cerebrospinal fluid	11.4 μg/L
Urine, 24 hr	1,187 μg/L
Ikeda et al. [8]	
Serum	>400 μg/L
Tower [10]	
Patient 1	
Serum	122 μg/L
Cerebrospinal fluid	2.2 μg/L
Synovial/pseudotumor	3,200 μg/L
Patient 2	
Serum	23 μg/L
Synovial/pseudotumor	3,300 μg/L
Mao et al. [10]	
Patient 1	
Serum	410 nmol/L[b]
Cerebrospinal fluid	9 nmol/L[c]
Synovial/pseudotumor	4,218 nmol/L[d]
Patient 2	
Serum	258 nmol/L[e]
Pelclova et al. [12]	
Serum	506 μg/L
Cerebrospinal fluid	8.5 μg/L
Urine, pre-chelation	138.6 μg/L
Urine, during chelation	305 μg/L
Pericardial fluid	930 μg/L
Machado et al. [13]	
Plasma	230 nmol/L[f]

[a] Units as reported in the original paper
[b] Equal to 24 μg/L
[c] Equal to 0.5 μg/L
[d] Equal to 248.6 μg/L
[e] Equal to 15 μg/L
[f] Equal to 13.6 μg/L

Cardiovascular Dysfunction

Cobalt toxicity is classically associated with beer drinkers' cardiomyopathy, poisoning secondary to consumption of beer containing excess cobalt [18]. One case series of this condition included 28 men who developed severe congestive heart failure secondary to cardiomyopathy. Five developed atrial fibrillation or flutter and 11 died [19]. Our review only identified one case of biopsy-confirmed cardiomyopathy. Abnormal echocardiograms were documented in five cases and two patients developed atrial fibrillation; however, baseline echocardiograms were not available for review in published cases. Similarly, a study of Finnish cobalt workers

revealed that cumulative cobalt exposure was associated with subclinical echocardiographic changes [20]. Cobalt-induced myocardial injury has also been implicated in hard metal workers [21–23].

Neurological Dysfunction

Historically, neurotoxic symptoms such as hearing loss, visual impairment, and polyneuropathy were attributed to cobaltous chloride infusions [24–26]. Although most of the neurologic symptoms described in our review are highly subjective, neurologic dysfunction was objectively demonstrated as optic nerve atrophy (three cases), audiometry-documented hearing loss (four cases), and abnormal electrodiagnostic studies (three cases). Overall, a neurologic symptom was reported in 9/10 cases. Cobalt neurotoxicity is controversial and its mechanism is not clearly established. Proposed mechanisms include disruption of mitochondrial oxidative phosphorylation, neurotransmitter modulation, and direct neuron cytotoxicity [27].

Proposed Mechanisms of Toxicity

Similarly, a unifying mechanism of cobalt toxicity in general has not been identified. The histopathologic changes in beer drinkers' cardiomyopathy have been attributed to cobalt's high affinity for sulfhydryl groups resulting in impaired oxidation of Krebs cycle intermediates, transmembrane transport system damage resulting in increased intracellular calcium, and chronic inhibition of sympathetic tone [18, 28]. Epidemiologic studies suggest that concomitant malnutrition may be required for cobalt-induced cardiomyopathy [29]. Although controversial, thyroid dysfunction has been attributed to cobalt's inhibition of tyrosine iodinase [15, 16, 30]. Studies of patients in the 1970s with the McKee cobalt–chromium–molybdenum prosthetics attributed "cobalt toxicity" to hypersensitivity as prosthetic failures were associated with positive cobalt patch testing [31, 32]. More recently, metal ion effects on cell-mediated immunity, lymphocyte reactivity, and chemokine secretion have been demonstrated [33–35]. Interestingly, in a patient with sensory polyneuropathy identified by our search, sural nerve biopsy revealed "moderate axonal degeneration with no inflammatory changes," suggesting that inflammation of nerves may not completely explain neurotoxicity [8]. Another patient identified by our search exhibited hyperintense lesions on brain magnetic resonance imaging (MRI) suggesting demyelination [7, 27]. Comprehensive reviews of cobalt's pathologic mechanisms are available elsewhere [27, 28, 33, 34, 36].

Co-HP components may also contain varying amounts of chromium and molybdenum. The contribution of other metals to suspected PHACT is unknown. However, the chromium of Co-HP exists in the trivalent state and is unlikely to be physiologically converted to the toxic hexavalent state [37]. In vitro studies of metal nanoparticle behavior have shown that nanoparticles liberate more cobalt ions than chromium ions, and cobalt nanoparticles are considerably more cytotoxic to cultured cells [38]. The molybdenum content of Co-HP is about one tenth that of cobalt and is not thought to play a role in suspected PHACT [39].

Clinical Features of Suspected PHACT

Our search identified patients with symptoms consistent with historic cobalt toxicity and elevated cobalt values in one or more matrices as summarized in Table 3. Studies comparing clinical and laboratory features of patients with Co-HP who develop suspected PHACT to asymptomatic patients with Co-HP have not been performed. Although risk factors for excessive metal ion release from Co-HP have been identified, no prognostic indicators for asymptomatic patients who may develop suspected cobalt toxicity have been studied [40]. Therefore, no definitive conclusions can be drawn regarding the association of suspected PHACT with specific patient historical, physical, laboratory, and imaging features based on the available evidence.

The testing and interpretation of cobalt values is controversial. Serum values are commonly reported and are most representative of extracellular fluid levels. However, some suggest that whole blood values more accurately measure systemic exposure [41]. A conversion equation for serum and whole blood values may prove clinically useful after independent validation [42]. One study found a linear correlation between pseudotumor aspirate values and serum cobalt values [43]. Further, urine and serum cobalt values appear to correlate once exposure is removed in workers occupationally exposed to cobalt dust [44]. Patients with Co-HP frequently have higher serum cobalt concentrations than industrial workers. It is unclear when elevated cobalt values should be considered potentially toxic because no clear correlation has been found between serum concentrations and physiologic effects [45]. Serum cobalt concentrations >5 μg/L are listed as likely toxic in one reference text although data supporting this threshold is lacking [46]. The FDA cautions that the interpretation of cobalt levels in patients with metal-on-metal hip implants has not been clearly defined and provides guidance regarding metal ion testing methodology [3]. Use of inductively coupled mass spectrometry for metal ion value determination is preferred [3, 47, 48].

Published Recommendations for Management

Regulatory agencies in the UK and USA have issued recommendations for both asymptomatic and symptomatic patients with elevated metal ion levels. The FDA defines "symptomatic

Table 4 Summary of FDA recommendations for orthopedic surgeons

	Symptomatic[a] patients	Asymptomatic patients
Regular clinical evaluation	At least every 6 months	Typically at least once every 1 to 2 years
Soft tissue imaging	Consider the benefits and risks of MRI, CT, and ultrasound for each patient	Not necessary if you feel the hip is functioning properly
Metal ion testing	Consider monitoring serial metal ion levels. Currently, the most reliable test results are available for cobalt in EDTA-anticoagulated blood[b]. In repeat tests, use same sample type, measurement method and preferably the same laboratory	Not necessary if you feel the hip is functioning properly

Table available online at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm335775.htm

[a] The FDA defines "symptomatic" as experiencing local symptoms (i.e., pain or swelling at or near the hip, a change in walking ability, or noise from the hip) more than 3 months after placement of a metal-on-metal hip prosthetic

[b] For chromium testing, a validated method that resolves potential interferences must be used. Please review FDA's recommendations for chromium testing [3]

patients" as those experiencing local symptoms (i.e., pain or swelling at or near the hip, a change in walking ability, or noise from the hip) more than 3 months after placement of a metal-on-metal hip implant and recently issued "Information for Orthopaedic Surgeons" [2]. The FDA advises surgeons to consider the patient's overall clinical presentation including symptoms, physical findings, and other diagnostic results when determining treatment scenarios; a summary of this guidance is reproduced in Table 4. Specific guidance for specialists to whom patients with evidence of systemic symptoms may be referred was not part of this communication [4]. The FDA's advice for other health care professionals caring for patients with metal-on-metal hip implants is summarized in Table 5. While the FDA provides detailed information on metal ion testing and interpretation on their website [3], it does not provide specific metal ion values that should trigger action. Conversely, the recommendations issued by the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) provide actionable thresholds summarized in Tables 6 and 7 [1]. The MHRA utilizes a cobalt value of 7 μg/L for medical decision making. However, the impetus for their inquiry leading to these recommendations was an increase in device failure, not to address patients with systemic toxicity. Further, this 7 μg/L threshold was derived from a population reference range, not comparison data between symptomatic and asymptomatic patients [49]. Most asymptomatic patients with Co-HP will have stable cobalt levels up to 10 μg/L and few develop toxicity [43]. The FDA has recommended consideration of serial metal ion testing in symptomatic patients and advises interpretation of these levels in the context of symptoms, baseline renal function, and the potential for alternative sources [2, 3]. Therefore, the cobalt value of concern is unknown. Following value trends, in lieu of absolute values, may be more informative during patient evaluation.

No consensus has been reached in regard to treatment of patients with systemic symptoms. These patients have been treated supportively. Some patients identified by our methods received thyroid replacement and corticosteroids but clinical response is inconsistently documented [6, 7]. Machado et al. reported a "good clinical response" to beta-blockade, ACE inhibition, and diuresis in their patient with cardiomyopathy [13]. Little evidence exists to inform decisions about enhanced elimination of cobalt in cases of suspected PHACT. Pelclova et al. described a patient 14 months after receiving a Co-HP;

Table 5 Summary of FDA recommendations for other health care providers

Be aware of possible metal ion adverse events	Recommended action
Possible systemic symptoms in patients with metal-on-metal hip implants:[a] • General hypersensitivity reaction (skin rash) • Cardiomyopathy • Neurological changes including sensory changes (auditory or visual impairments) • Psychological status change (including depression) • Renal function impairment • Thyroid dysfunction (including neck discomfort, fatigue, weight gain, or feeling cold)	Patients with systemic findings that are thought to be related to a metal-on-metal hip implant should be advised to follow-up with his or her orthopedic surgeon to determine the appropriate course of action

Adapted from information available online at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm335775.htm

[a] FDA notes that these symptoms are based on case reports in the literature

Table 6 MHRA management recommendations for symptomatic patients with metal-on-metal hip replacement implants

	MoM hip resurfacing (no stem)	Stemmed MoM total hip replacements —femoral head diameter <36 mm	Stemmed MoM total hip replacements —femoral head diameter ≥36 mm	DePuy ASR™ hip replacements (all types)
Patient follow-up	Annually for life of the implant			
Imaging: MARS MRI or ultrasound	Recommended in all cases			
First whole blood metal ion test	Yes			
Result of second whole blood metal ion test	Level >7 ppb[a] indicates potential for soft tissue reaction			
Second whole blood metal ion test	Yes, 3 months after first test if result >7 ppb			
Results of second whole blood metal ion test	Level >7 ppb indicates potential for soft tissue reaction, especially if greater than previously			
Consider need for revision	If imaging is abnormal and/or whole blood metal levels rising			

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MARS metal artifact reducing sequence, *MHRA* Medicines and Healthcare products Regulatory Agency, *MoM* metal-on-metal

[a] Seven parts per billion (ppb) equals 7 μg/L or 119 nmol/L for cobalt

20 months after implant his serum cobalt was 506 μg/L [12]. The patient received 15 total doses of 2,3-dimercaptopropane-1-sulfonate (unithiol); his urinary cobalt excretion increased and his serum cobalt level decreased by 26 %. The authors noted that his symptoms improved except for hearing loss but, ultimately, hardware removal was performed. Ikeda et al. described a patient 2 years after Co-HP implantation; the blood cobalt concentration was >400 μg/L [8]. At the time of revision surgery, the patient had a single treatment with hemodiafiltration but no post-procedure value is provided. Finally, Pazzaglia et al. described a patient 1 year after receiving a Co-HP; whole blood cobalt was 550 μg/L [11]. The patient received 70 days of EDTA (one dose every 7 days) between diagnosis and hardware removal. The patient's whole blood cobalt value declined with the first two doses, followed by subsequent rise. Rebound between doses was attributed to ongoing release from the hip surface. Rebound and metal redistribution are known risks of chelation therapy. In animal models of cobalt toxicity, chelating agents were able to reduce total body cobalt values through reduction of hepatic and renal cobalt stores. However, there was no difference in brain cobalt values between chelated animals and untreated controls. Further, two chelating agents actually increased heart values [50]. Similarly, this chelation-associated redistribution of toxic

Table 7 MHRA management recommendations for asymptomatic patients with metal-on-metal hip replacement implants

	MoM hip resurfacing (no stem)	Stemmed MoM total hip replacements —femoral head diameter <36 mm	Stemmed MoM total hip replacements—femoral head diameter ≥36 mm	DePuy ASR™ hip replacements (all types)
Patient follow-up	According to local protocols		Annually for life of the implant	
Imaging: MARS MRI or ultrasound	No, unless concern exists for cohort or patient becomes symptomatic		Recommended if whole blood metal ion levels rising	Recommended in all cases
First whole blood metal ion test	No, unless concern exists for cohort or patient becomes symptomatic		Yes	
Result of first whole blood metal ion test	Not applicable		If level >7 ppb[a] then second whole blood test required 3 months later	
Second whole blood metal ion test	Not applicable		Yes, 3 months after first test if result >7 ppb	
Results of second whole blood metal ion test	Not applicable		If whole blood metal ion levels rising further investigation required including imaging	Whole blood metal ion level rising indicates potential for soft tissue reaction
Consider need for revision	Not applicable		If imaging is abnormal and/or whole blood metal levels rising	

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MARS metal artifact reducing sequence, *MHRA* Medicines and Healthcare Products Regulatory Agency, *MoM* metal-on-metal

[a] Seven parts per billion (ppb) equals 7 μg/L or 119 nmol/L for cobalt

metal from relatively "safe" tissues into more susceptible tissues has been noted in animal models of lead toxicity [51]. More robust studies of enhanced elimination strategies in suspected PHACT are warranted.

Natural Course of Suspected PHACT

Little information is available regarding the course of cobalt-containing hip-associated toxicity. Historically, patients with thyroid dysfunction after treatment with cobaltous chloride made full recoveries once treatments were discontinued [30]. However, neurologic symptom resolution has been variable. In a patient with iatrogenic cobalt toxicity from treatment of anemia, nerve deafness and vertigo resolved 4 months after dosing with cobalt stopped [26]. Similarly, high-frequency hearing loss in two hemodialysis patients with refractory anemia resolved 1 month after cobaltous chloride treatment was discontinued [24]. Conversely, in a patient who developed optic atrophy, no progression of disease was noted after cessation of cobalt therapy but no recovery was observed either [25]. Mao et al. followed two patients after Co-HP hardware removal. Symptoms gradually improved and appear to correspond to decreasing blood cobalt levels; however, complete resolution was not achieved by 8 weeks in either patient [10]. Oldenburg et al. reported one patient whose symptoms had improved within 6 months of hardware removal [6]. Unfortunately, "in long-term follow-up, the patient's neurologic symptoms [had] persisted." One patient identified in our review developed dyspnea 6 years after receiving a Co-HP. The patient, diagnosed with PHACT and cardiomyopathy, improved symptomatically with concomitant ejection fraction increase from 21 to 45 % after hardware removal [13]. Similarly, Tower reported subjective improvement in exercise tolerance, dyspnea, and diastolic dysfunction 11 months after hardware removal [9]. Oldenberg et al. did not specifically comment on cardiac symptom resolution in the sole biopsy-proven case of cardiomyopathy identified in our review [6]. Typical symptom duration with suspected PHACT appears to vary. Nine of 10 case report authors identified by our search reported patient symptom course after hardware removal during follow-up periods ranging from 1 to 18 months. All reported symptom improvement after hardware removal. Quantitating improvement requires comparison of studies performed preexposure, during patient exposure, period of greatest symptoms, and post-hardware removal. These studies have not been performed, making definitive statements about the course of PHACT, as well as, causation problematic.

Limitations

Several limitations of this review should be mentioned. As no formal case definition exists, our search strategy may have failed to identify all cases. We excluded patients with isolated local joint symptoms like pain. It is possible that some of these patients' pain is secondary to neurotoxicity. Additionally, we cannot rule out the possibility of publication bias; patients identified by our methods may be outliers. Further, as only 10 cases were available for systematic review, these patients may not be representative of all patients with Co-HP and their clinical presentations may not be representative of all patients with suspected PHACT. Further, because no comparative data between symptomatic and asymptomatic patients with Co-HP exist, we relied on review of case reports, the least robust form of evidence. We attempted to minimize these limitations by adhering to guidance for systematic review methodology published in the general and toxicology literature [14, 52, 53].

Conclusion

As the number of patients with suspected PHACT increases, medical toxicologists are likely to become involved in their care. This systematic review summarizes the clinical presentations of patients with suspected PHACT. The information currently available regarding patients with suspected PHACT is inadequate to guide clinical decision making at this time. No consensus has been reached regarding the management of asymptomatic Co-HP patients with elevated cobalt levels. No consensus has been reached regarding the management of Co-HP patients with systemic symptoms. Indications for chelation have not been established and require further study. There are no reliable data suggesting chelation therapy for suspected PHACT is efficacious; its routine use should be discouraged. Improved case definitions, improved surveillance, and controlled studies are needed to elucidate the scope of this problem and guide future investigations.

Conflict of Interest The authors report no declarations of interest. The opinions in this Review are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry. Dr. Brent reports that he has provided background scientific research as a paid consultant for DePuy Companies.

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