**Arthroprosthetic Cobaltism is Common**
A screening study of 241 patients with joint replacements with Urine-Cobalt and Cobaltism-Symptom-Inventory (CSI)

**Utility of FDG-PET Brain Scanning in the Diagnosis of Arthroplasty Cobalt Encephalopathy**
Neuro-Q analysis of 69 FDG-PET Brain Scans in neurologically symptomatic cobalturic patients shows brain hypometabolism c/w Chronic Toxic Encephalopathy

8.5 minute public testimony 11/13/19
FDA Expert Panel

Stephen S. Tower, M.D.  Affiliated Professor UAA/ WWAMI
Robert Bridges, M.D. Diagnostic Radiology and Nuclear Medicine
Christina Cho, BA Research Assistant TOJRC
Bradford Gessner, MD, MPH Epidemiology and Vaccines

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Disclosures

Index Case of Arthroprosthetic Cobaltism from modern MoM Hip replacement 2006-2009

Author of Index Case Reports: AK State Epi, Alaska Medicine, JBJS 2010. Now about 10 other peer-reviewed publications on various aspects Arthroprosthetic Cobaltism

As surgeon has implanted about 2000 “AT RISK” Joint Replacements

No commercial Conflict-of-Interest

Son-in-Law is an Arthroplasty Design Engineer

Settled Litigation with J&J concerning own ASR MoM Hip

Compensated Legal Expert in one case concerning cobalt-chrome hip metallosis complications. I was primary and revision surgeon. Gross compensation to date for this work $28,500 for 57 hours. > 20 hours spent complying with Subpoena Duces Tecum
Primary Immune Presentation:
Monoclonal Gammopathy (IGA), Oat Allergy, Tremor, Peripheral Neuropathy, Cognitive Decline, Irritability

46 y/o Executive at 1* THA, 2009 Zimmer Kinnectiv MoP Hip, Severe Immune GI Syndrome, Oat Allergy, Mast Cell Activation Syndrome, Later Onset of hip pain, Fatigue, Cognitive Decline, B[Co] = 2.4 ppb, U[Co]=8.0, Monoclonal IGA, FDG PET (-97, 9 clusters), MS MRI Hip pseudotumor, Hips Revised to Ceramic-on-Plastic, 3 months post revision B[Co] = 0.7, U[Co]=1.5, Improved Cognitive Function, Bone Marrow Pending
Arthroprosthetic Cobaltism

Clinical Syndrome (REVERSABLE!)

- Fatigue
- Cognitive decline
- Disordered mood
- Motor and Sensory Dysfunction
- Immune Syndrome
- Cardiomyopathy
- Periprosthetic Adverse Reactions to Metallic Debris

Pathophysiology

- Suppression of cellular metabolism
- Immune reaction to cobalt (periprosthetic and systemic)

Imaging

- 18-F-FDG PET Brain scan
- Cross-sectional Imaging of prosthetic Joint
“at-risk-joint”

A hip, knee, or shoulder replacement with any Chrome-Cobalt (CrCo) part regardless of bearing couple

- Metal-on-Metal (MoM) resurfacing and stemmed, CrCo Head and Socket
- Metal-on-Plastic (MoP) Modular CrCo Head
- Some Ceramic-on-Plastic hip designs with modular CrCo necks, stems, or sockets
Alaskan 241/139/102/69 Series
Screened with Urine-Cobalt and
13 symptom inventory

- 241 patients with an “at-risk-joint” screened over 48 months
- 139 Cobalt-Positive (\(U[\text{Co}] \geq 1\) ppb or \(B[\text{Co}] \geq 0.4\) ppb) 102 Cobalt-Negative
- 69 of 139 Co+ patients with confirmed Arthroplasty-Cobalt-Encephalopathy (ACE) by FDG-PET-Brain-Scan
13 symptom inventory
(incidence in Co+ patients, p value)

- Tremor (77%, p<0.0001)
- Forgetfulness (59%, p<0.0001)
- Fatigue (55%, p<0.0001)
- Imbalance or Weakness (47%, p<0.0001)
- Disordered Mood (53%, p<0.0001)
- Disordered Sleep (35%, p<0.001)
- Chronic Pain (26%, p<0.001)
- Audiovestibular dysfunction (33%, p=0.0028)
- Peripheral Neuropathy (18%, p=0.0003)
- Non-refractive Blindness (15%, p=0.0005)
- New non-ischemic CV problem (27%, p=0.0002)
- New Immune problem (15%, p=0.012)
- Symptoms at replaced joint (60%, p=0.006)
MoM Articulation
N=37, Mean U[Co]=54.0

Not-MoM Articulation
N=194, Mean U[Co]=5.4
p<0.001
MoP High Risk Z12/14, S V40, DMA, MN
N=142, Mean U[Co]=6.4

MoP Low Risk OC, BT, N&S12/14, D12/14
N=18, Mean U[Co]= 0.9 p=0.034
20 Revised ACE Patients

- 16 followed greater than 6 months post-revision
- 16 of 16 improved cobaltemia and cobalturia
- 12 of 16 notably improved ACE symptoms
- 1 of 16 notably worse dementia one year post-revision
37 Patients with FDG/PET Brain Scan

- Analysis with NeuroStat and Neuro Q software
- All brains significantly hypometabolic compared to age and gender matched normal
- A brains show pattern of hypometabolism consistent with Chronic Toxic Encephalopathy (CTE) described in solvent exposure, heavy metal exposure, carbon monoxide poisoning, and “chemo brain”
- CTE pattern of hypometabolism is distinct from than described for Alzheimer's, Lewy Body, and Frontal-Temporal dementias and that noted for Parkinson’s disease.
37 Patients with FDG/PET Brain Scan
Sort into 3 groups relating to sensitivity of the patient to
Arthroprosthetically Generated, Systemically Circulated COBALT
SEVERE HYPOMETABOLISM GENERALIZED and FOCAL

- MEDIAL TEMPORAL LOBES
- ANTERIOR CINGULATE GYRUS
- BASAL GANGLIA
- DISCRETE AREAS OF
  - FRONTAL
  - PARIENTAL
  - OCCIPITAL CORTICES

NEUROCONGITIVE DEFICETS

- SHORT TERM MEMORY
- PROCESSING SPEED
- WORD FINDING DIFFICULTIES
- MOTOR SPEED
- FINE MOTOR COORDINATION
- DISORDERED MOOD
- FATIGUE AND DISORDERED SLEEP
10 Patients with Repeat FDG/PET Brain Scan

- 8 patients 6-12 months post revision surgery with improved cobaltemia
  - 4 clinically improved patients had significantly improved scans at 6-12 months
  - 1 clinically stable patient’s scan was notably improved at 18 months post-revision.
  - 2 clinically worse patients’ scans were worse at 6 months post revision.

- 2 patients not revised had repeat scans at 18 months after first scan
  - 1 with decreased cobaltemia had an improved scan.
  - 1 with increased cobaltemia had a worse scan
Cobaltism Awareness:

Cobaltism may precede Hip Symptoms

46 y/o Pilot F/H PD
2009 Biomet “Magnum” MoM Hips
42 months max DBS & Drugs
Onset of hip pain B[Co] = 116 PPB
Hips Revised to Ceramic-on-Plastic
2 months post revision B[Co] = 0.7
12 months post-op off DBS & Drugs
2 years post-op off Drugs, lowest DBS setting

510K MoM Hip
Not recalled
Cobaltism Awareness:
Systematic Monitoring of Patients with Most Hip Replacements Indicated

40 y/o nurse, missed 2 annual follow-ups but saw surgeon vocationally 1-2 times a week
[BCo] = 63 ppb
Reversible Neurocobaltism with 48 months of surplus morbidity
Cobaltism Awareness: Systematic Monitoring of Patients at Risk for Taper Corrosion Indicated

Rejuvenate Implanted 8/2010
70 YO GENERALLY WELL WOMAN
20 months later:
progressive fatigue, poor sleep, nausea, weight loss from 140 to 120 pounds, deafness, myalgia, cognitive decline, arrhythmia and diastolic dysfunction
B[Co] = 11 PPB

Recalled 7/2012 (at 23 months)
Explanted after 33 months
Cobaltism Awareness: Systematic Monitoring of Most Patients with Replaced Hips or Shoulders is Indicated

Stryker Accolade “fitted” 2006 for a 68 year-old Professor
8 years later onset of progressive cognitive decline, tremor, fatigue, incoordination, and

B[Co] = 5.8 PPB
U[Co] = 35 PPB
Joint Fluid [Co] = 1100 PPB

Neurocognitive testing unfit to drive due to incoordination, reaction time, and judgment issues. Revised 8/2016 patient now 78 YO.

“Silent Recall” V40 Taper CrCo heads 10/2016
Acetabular Side MACC MDM and MoM
Periprosthetic Consequences of Chrome-Cobalt Metallosis

Pseudotumors
and
Necrosis of Capsule, Tendons and Bone
leading to
Hip Instability
Weakness
Prosthetic loosening
can be
Painful or Painless
Systemic Consequences of Chrome-Cobalt Related Cytotoxicity

**Toxic Progeria**

Oxidative Stress and Mitochondrial Toxicity

leading to

Death or Dysfunction of Highly Metabolic Cells

resulting in

Mood and Sleep Disorders
Constitutional and Cognitive Decline
Motor-Sensory Neuropathy CNS & PNS
Audio-vestibular and Optic Dysfunction
Movement Disorders
Cardiomyopathy
Immune Dysfunction
Monitoring Hip Patients at Risk

**Blood or Urine** Cobalt (PBB)

- **0.1** NORMAL
- **1** BIOLOGIC EXPOSURE THRESHOLD (BET)
  - > **0.4** Nearly all MoM, MOST MODULAR CrCo Modular Neck
  - > **0.4** Many (10-50%) MODULAR CrCo Modular Head MoP Hips
- **0.4-10** Pseudotumors, subclinical and mild COBALTISM
- **11-100** subclinical, mild, and moderate COBALTISM
- **101-300** moderate to severe COBALTISM
- **301-1000** extreme COBALTISM (30 CR), DEATH (5 cases)

Cobalt debris from corrosion a order of magnitude more toxic than that produced by abrasive wear.

Urine levels generally 2.5 X Blood Levels
Dose Response of $U[Co]Years$ to CSI Score