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Title: Chronic Fatigue Syndrome: is Cadmium the Catalyst?

Abstract

Understanding the actions of cadmium may well be one of the keys to understanding CSF. Low dose Cd toxicity can be suspected by looking for historical evidence of genetic susceptibility to disease, nutritional deficiency, psychosocial stress, and other toxic exposures that could be synergistic with Cd. Laboratory studies indicate stress phenomenon. To further understand the role of Cd in CFS, research is needed on platelet reactivity, nutrient levels, beta-2 microglobulins, and ultrastructural studies of nerves, muscle and connective tissue.

Key Words: Chronic Fatigue Syndrome, Cadmium Toxicity, Psychoneuroimmunology

Introduction

Using existing assumptions it has not been possible to identify the cause of chronic fatigue syndrome [1]. It is possible that the methods of investigation and the proofs being sought are not appropriate. Cd is a highly toxic agent in cell culture and in aquatic environments and yet there is no conclusive proof that is linked to human disease, except in circumstances of industrial exposure. Since in cell systems the levels of free Cd that can cause a toxic effect are ones that occur in ambient exposures, it is possible that Cd plays some role in CFS but this can't be recognized with existing methods of direct scientific proof.

Indirect methods and an interdisciplinary synthesis of research facts must be used to implicate Cd's involvement. The ways in which Cd could influence CFS are varied and enmeshed. It is possible that the individuals who contract the disorder are experiencing toxic effects from the exposure to Cd either in the air, dust, or food. Stresses, such as viruses or other micro-organisms that are synergistic with Cd or nutritional deficiencies that could come from chronic Cd toxicity, could be playing a role as well.

Chronic viral infections can produce a vast array of problems [2] that also can be produced by Cd [3]. Several studies suggest that the role of immuno-competent cells needs to be examined in CSF [4,5,6]. Cd has profound effects on immune cells [7,8].

The toxicity of the air exposures could be influenced by other air pollutants such as the drop in lead and possible drop in zinc. In local areas significant co-pollutants could play a role or local deficiencies could affect Cd toxicity. All organism are affected by Cd and bacteria exposed to Cd rapidly develop Cd resistance by acquiring plasmids that pump the ion out of the cell or by producing polysaccharides that bind Cd, inactivating it [9].

Recent studies have shown that low doses of free Cd have profound effects on multiple cell regulatory processes. Smith et al. have found that there is a Cd sensitive cell surface receptor, antagonized by zinc and lead, which activates protein kinase C and mobilizes calcium from the endoplasmic reticulum [10]. Verbost et al have found that Cd has 1000 times more affinity than calcium for the calcium ATPase enzyme on cell membranes [11]. Inhibiting the enzyme also increases intracellular calcium which in turn stimulates a variety of stress responses.

Normally, Cd is bound and little free Cd is present. Glutathione and metallothionein are primary cellular defenses against Cd [12]. In a catabolic state, such as during a prolonged infectious illness, however, Cd is released from metallothionein, principally from stores in the liver. Cd releases endogenous glucocorticoids, which have been found to inhibit human natural killer cell activity [14], a finding in CFS. Stress is known to deplete the body of many essential vitamins and minerals. It is quite possible that this is mediated through the release of Cd.

Emotional stress evokes marked changes in animals that would be found with release of free Cd [15]. It is possible that Cd is the biochemical link between psychosocial stress and disease. Certainly social stress and Cd exposure have interactive effects. Drummond (US EPA, personal communication) has found that 12ug/L of Cd kills trout (a normally solitary fish) housed in groups in tanks, while it is possible to increase to 1,600 ug/L Cd when the trout are housed individually.

There is no specific marker for a Cd toxic effect at low dose. It is necessary to carefully evaluate the situations in which the syndrome evolves, looking for evidence of vitamin and mineral deficiency, searching for exposure to a variety of

stressors, and considering a variety of deviations from the mean on laboratory tests as indicators of free Cd. In this paper I will review the literature relating Cd mediated effects that may have a bearing on CFS, discuss the implications for assessment and treatment of CFS, and, finally, address the issue of "scientific" proof.

Literature Review

The presence of muscular pain proceeding to muscle injury and weakness is a frequent finding in CFS [1,5]. Renee Toury has found that chronic exposure of rats to Cd produces injury in muscles [16]. These effects are identical to those found when the animal is calcium and vitamin D deficient. These deficiencies in turn can be severely aggravated by low dose chronic Cd exposure [3].

The predominance of females is striking [4]. In low dose exposure of rats to metals, lead was protective to females [17]. Cd produced a number of toxic effects in multiple organ systems. Cd uptake into certain cells is strongly influenced by estrogen [18]. Cd has a significant effect on steroid metabolism, interfering with testosterone formation in the toad [19]. Males frequently have a low vitamin C level, which is a marker of a Cd toxic effect, so that females are not the exclusive victims.

To understand the behavior of a metal like Cd in the environment it is essential to consider the presence of the total mixture of substances in which it is occurring [20]. In this decade there has been a tremendous drop in air lead from 1.5ug/m^3 to 0.04ug/m^3 due to the elimination of lead from gasoline. Showman has found that in lichens there has been a significant drop in zinc levels [21]. Both lead and zinc block Cd binding to the Cd sensitive cell receptor [10]. The change in air pollution has increased Cd effects on cells. The ramifications of these changes are immense [22]. By blocking zinc uptake by plants and the transpiration of zinc into the atmosphere [23], where it would normally block Cd, the problems intensify.

The effects could be indirect. The drop in lead could increase the growth of yeast, since lead breaks tRNA of yeast at very low levels [24]. The yeast endotoxin could be synergistic with Cd. Bacterial endotoxin has been demonstrated to be toxic to animals in the presence of Cd and prednisone, while lead is protective in that circumstance [25].

A decrease in stomach acid and the use of antibiotics and alcohol appear to predispose to mycelial yeast [26-29]. Fungemia produces transient toxic effects in normal persons [30]. Chronic yeast infections appear to predispose to loss of parietal cell function and hypofunction of multiple endocrine organs [31]. The role of Cd in converting yeast to the mycelial form has not been directly studied, but based on Cd's known actions and the predisposing factors, it is possible that it plays a role.

Cd is the most toxic metal in water [32] and air [33]. When combined with copper or chlorinated compounds non-toxic doses of Cd become toxic [20,34,35]. Since the level of Cd associated with chronic toxicity is only 5 fold higher than background levels, it is clear that local pollution conditions could increase background levels to toxic levels. Levels of Cd in phytoplankton are quite high in July [36], possibly from the transpiration of Cd from plants [23]. Combining these air exposures, which contribute strongly to body burden [37] with chloroform, which is ubiquitous in chlorinated drinking water, one could produce a synergistic toxic effect, as found in hepatocyte culture [35].

CFS is associated with depression [38], and many investigators believe that it is a psychiatric problem. Cd has many effects on the brain. Neurohormones and peptide growth factors bind to the Cd sensitive cell surface receptor [16,39]. Certain effects of Cd on the brain involving lipid metabolism [40] are very similar to a neuropathy caused by B-12 deficiency [41]. Multiple neurological problems in humans are compatible with changes found with B-12 deficiency [42]. B-12 co-enzymes normalized lipid peroxidation in liver microsomes of rabbits poisoned with phenylhydrazine. Aniline detoxifying enzymes were involved [43]. It is possible that B-12 acts to detoxify Cd, reversing the inhibition of detoxification enzymes in the liver [44].

One effect of Cd is the production of auto-antibodies [45], which could be involved in the muscle injury. The CFS has some similarities to disease of auto-immunity. Cd and mercury, but not lead, are capable of causing auto-immune disorders [46]. Of the two, Cd is the more potent immune modulator [47].

Vitamins and minerals play a significant role in immune status [48]. Viral persistence occurs in the presence of immune dysfunction. Pharikal considers vitamin C deficiency a metabolic marker of a Cd toxic effect [49]. Another nutrient depleted by Cd and stress is B-12, which is lost from muscle in hemorrhagic stress [50]. Zinc, selenium, and vitamin E are important in maintaining cellular immunity [48]. All three are protective against Cd. Vitamin E has been noted to protect the brain [51]. All can be depleted with chronic Cd exposure because Cd increases free radicals.

Detecting Cadmium Toxic Effects in CFS

Although there are reasonable grounds for suspecting that Cd is involved in the disorder, in plant and animal studies there is no specific marker of a Cd toxic effect [52]. However, by studying in detail the effects of Cd isolated in cell culture and organ systems, it is possible to develop strategies to detect Cd effects in humans. Although these methods do not provide certainty, they do provide information relevant to the assessment and treatment of individuals afflicted with CFS.

There are many genetic factors which control the susceptibility to Cd toxic effects [53,54]. A detailed history is one of the most useful means of detecting susceptibility to Cd mediated effects. Cd is linked in animal studies to essential hypertension, heart disease, cancer, learning or behavioral problems, and degenerative diseases of various kinds [3,13]. A history of such diseases suggests a susceptibility to Cd toxic effects. In a sublethal dose Cd can induce protective reactions and increase survival as well as lead to disease and death. Deviation of longevity from the mean in both directions may indicate susceptibility to Cd.

It is possible to estimate the exposure to Cd in air, food, and water. However, evidence of psychosocial stress is extremely important for it is the stressor which is particularly potent in freeing Cd. The level of nutrient intake which could potentially block the effects of exposure also needs to be assessed. Many nutrients are capable of blocking Cd toxic effects. They have different targets as well. A nutrient dense diet consisting of fresh fruits, vegetables, seeds, and nuts provide the vitamins, minerals, antioxidants, and essential fatty acids that can block Cd toxicity. Milk, on the other hand, increases Cd toxic effects [55]. This effect can be blocked with plant fiber and fish oils. Geological variations may affect the availability of other key nutrients such as selenium, iodine, cobalt, and chromium.

In the history of the individual, frequency of infections, deviation of developmental landmarks, and deviations of growth are indicators of possible Cd effects.

On physical exam, evidence of nutritional deficiencies such as dry skin, zinc lines in the fingernails, parakeratosis, the presence of chronic viral or fungal infections or intestinal parasites which are common with nutritional deficiencies are evidence of Cd toxic effects on the immune system. There may be a deviation of BP from the mean. Increases in systolic and diastolic pressure may be found. Reflexes may be increased or decreased.

Using a complete blood count (CBC) and chemistry profile 23 it is possible to find multiple deviations from mean values which are suggestive of Cd toxic effects. At very low doses Cd increases release of lactic acid dehydrogenase (LDH) from the liver in the presence of zinc deficiency [56]. Elevations of LDH are commonly seen with stress and are considered non-specific. It is just such non-specific changes that are characteristic of Cd. However, it is not always elevated. With increased intracellular calcium, there can be decreased expression of this enzyme on the cell surface and the level in blood may be low. Because of these divergent effects, it is necessary to consider increases in deviations from the mean as Cd indicators.

In children there is often an increase in inorganic phosphorus which is a characteristic Cd toxic effect in mammals [3]. However, hypophosphatemia can also be produced [57]. The alkaline phosphatase may be high or low. The LDL can be low [58], which is frequent in viral infections or high. The albumen can be depressed by Cd.

It is worthwhile inspecting the CBC. Cd causes an iron deficiency anemia which is associated with hypochromia and microcytosis [59]. However, stress depletes B-12 and leads to folate losses. Magnesium depletion decreases B-1. All of these changes cause macrocytosis. By increasing cortisol it can cause a lymphopenia; but as an immune modulator associated with auto-immune effects and polyclonal B cell stimulation, it can cause lymphocytosis. It has strong effects on platelets which can cause either increases or depletions in blood platelet numbers [60].

In the urinalysis one can look for proteinuria and calciuria which can occur transiently in response to Cd [61].

In viral infections, hematologic malignancies, and Cd poisoning, one finds an increase in beta-2 microglobulins in blood [62]. What has not been considered is that Cd is involved in all these processes. It is quite possible that beta-2 microglobulin is a fairly sensitive marker of free Cd in the blood stream.

Cd is taken up by platelets and makes them much more reactive. In a recent article, researchers found that first trimester pregnant women who later developed pre-eclampsia had platelets which were hyper-responsive to arginine vasopressin [63]. The increased intracellular calcium in their platelets was demonstrated with flow cytometry using the dye fura-2. Studies are needed to determine if this is a Cd toxic effect on platelets.

Hair analysis is a much less expensive and accessible means of detecting Cd exposure and toxic effects. Exposure to airborne Cd was particularly well correlated to hair Cd in children [64]. Seasonal variation and differences in age and hair color cause the standard deviation of Cd to be very high [65]. Nevertheless, hair analysis is an excellent indicator of multiple effects on nutrient minerals. Strong deviations from the mean indicate exposure to a stress agent, which is the effect of low level Cd toxicity. Taking a detailed history is the best way of knowing what other agents may be acting synergistically with Cd in causing these stress responses.

Through these various approaches, one can gather evidence to implicate Cd; but the evidence is far from perfect. It is reasonable to go to all this trouble because it is possible to intervene to block Cd toxic effects using relatively low cost, non-toxic interventions. These interventions might not be considered without suspecting that Cd was involved in the

disease process being treated.

A Protocol for Assessing CFS

Environmental Assessments: Local evaluation of pollution sources such as waste incineration, industrial processes, superphosphate fertilizers, paper mills, copper fumes. Assessment of drinking water quality. Soil characteristics in affected areas. Evidence of Cd resistance or Cd accumulation in suitable micro-organisms.

Patient Assessments:

Baseline Studies of Patients: CBC, Chem profile 23, Hair analysis, UA. 25-Oh vitamin D levels.

Susceptibility Assessment: Complete history noting birth weight, prematurity.

Illness history from infancy to present. Severity of viral illnesses such as chicken pox.

Family History: genetic susceptibility to hypertension, auto-immune disease, cancer, cataracts, dyslexia, mental disorders, alcoholism, addiction problems, allergies, skin disorders.

Psychological Status: presence of anxiety, depression, or other mood disturbances. General feeling of well-being. Past or present psychosocial stress.

Social Status: Social support network, recreational opportunities, creative pursuits.

Nutritional Status: dietary preferences, evidence for allergies or food addictions, or intolerance.

Life Style: Exercise, caffeine, alcohol, or drug use.

Medications: use of estrogen, thyroid, cortisone, antibiotics, neuroleptics, or other substances that could interact with Cd.

Environmental Exposures: passive smoke exposure since conception. Current active or passive smoke exposure. Location of birth and childhood, noting pollution sources in air or water. Exposure to farm chemicals or other exposures during childhood, agent orange exposure, occupational exposure. Physical Status: age, detailed exam looking for nutritional deficits. Skin texture, stria, zinc lines, hair texture, fat deposition, muscle mass, fissures or coating on tongue, reflexes, tooth loss, dental fillings (silver amalgams), blood pressure, evidence of yeast overgrowth, fungal dermatitis.

On a case by case basis it is necessary to see whether host factors, infectious agents, or environmental contamination are playing a predominating role.

Therapeutic Interventions

There are many ways for patients to heal themselves (see Table 1). Through an understanding of psychoneuroimmunology, the physician can serve as a co-author and coach. Since stress is such an important activator of free Cd, stress reduction is a major therapeutic modality. Breathing, gentle stretching, and massage, particularly of reflexes to stimulate circulation and release of endorphins, are all helpful modalities. In my patients I have noted that many have traumatic past experiences and benefit from psychotherapy that involves healing the inner child. Meditative tapes that tap spiritual resources within can have a powerful influence.

Eliminating tobacco, chlorinated drinking water, caffeine, alcohol and processed food are helpful. A diet of fresh fruits, fresh vegetables, cooked vegetables, seeds, nuts, yogurt, and fish is recommended.

Vitamins, minerals, amino acids, traditional herbal remedies, and a variety of pharmaceuticals are effective in blocking Cd toxic effects, blocking its entry into cells, or fostering its safe excretion. Once one is alerted to the possibility of Cd toxicity, a large number of therapeutic options can be considered.

Vitamin depletion is one important characteristic of free Cd. Sufficient vitamins, minerals, and amino acids play a major role in immunity and they are also a major deterrent to toxic effects from Cd exposure. Since vitamin C is the principal anti-oxidant in extracellular space, supplementation in conditions of stress is necessary to prevent injury. Vitamin C also normalizes mucosal injuries produced by Cd.

The fat soluble vitamins are affected by Cd and supplementation can be helpful. Vitamin E blocks Cd toxicity in the brain [51]. In the presence of vitamin D deficiency the toxic effects of Cd are greatly exaggerated, so that supplementation is necessary if deficiency occurs. Cd decreases retinol binding protein which decreases vitamin A transport to tissues and increases the toxicity of dietary vitamin A. This toxicity is blocked by zinc, taurine, vitamin E and vitamin D [66].

The B vitamins work together with minerals. By causing stress, Cd leads to a depletion of magnesium, potassium, zinc and chromium. With chronic Cd exposure, iron, copper, and B-12 are lost from the liver. B-12 supplementation is helpful since it normalizes microsomal enzymes involved in liver detoxification which Cd disrupts [43,44]. Lipoic acid is helpful since it blocks Cd uptake and toxicity in the liver [67].

Magnesium is not absorbed well in the presence of Cd. Cd toxic effects on the small bowel cause malabsorption. Since thiamine is carried into cells with magnesium, a deficiency of B-1 is always present when there is magnesium deficiency. In order to restore magnesium to depleted cells, it is necessary to have sufficient vitamin D, E, essential fatty acids, digestive acid, folic acid, magnesium and B-1 just to get the magnesium across the intestinal epithelium into the blood stream. Potassium, zinc, and B-6 are necessary to facilitate its uptake into cells throughout the body.

Zinc is essential in blocking Cd toxic effects on the immune cells. Zinc protects the renal cells from Cd toxicity by inducing metallothionein. Swallowed zinc, however, is a strong stimulus of metallothionein in the intestinal cells which can block zinc uptake to other cells. Zinc lozenges may be more effective in bringing zinc to immune cells. At least in a study of zinc effects on rhinovirus, the lozenge was effective and the swallowed pill did not differ from the placebo control [68].

Selenium facilitates Cd excretion into bile [69]. Blood selenium falls with exposure to increased Cd. Cd binds to selenium forming an insoluble precipitate. Germanium has helpful immune modulatory effects, perhaps by facilitating Cd excretion into urine. Selenium and germanium are present in significant amounts in garlic, which has been used as an effective Cd chelator [70].

Cd iodide is also insoluble. Kelp and other forms of seaweed that are good sources of iodine are useful in blocking Cd toxicity.

Quercitin is a bioflavonoid found in many healing herbs. It has many complex effects that could influence Cd toxicity by acting as an anti-estrogen or anti-calmodulin [71].

N-acetyl-cysteine increases Cd excretion in the urine four fold [72]. It also increases glutathione, a central cellular defense against Cd and many other toxic agents. The extracellular cysteine concentration has a strong influence on the viability of cycling T cell clones [73].

Cd binds to calmodulin, replacing calcium and changing its function [74]. Anti-calmodulin drugs like phenothiazines protect certain organs like the testes from toxic effects of Cd. It is quite possible that they could protect brain cells from certain Cd toxicities, as well. Calcium channel blockers like nifedipine and verapamil block the uptake of Cd into endocrine cells, blocking its toxicity [76]. By blocking autonomic nervous system responses to stress, alpha and beta adrenergic blockers block Cd toxic effects associated with over-stimulation of the sympathetic system. Alpha and beta-agonists are helpful if this system is depleted or overpowered by competing stimuli. Drugs that normalize ion shifts across membranes like many of the anti-depressants also block an effect of Cd.

Recently Perry et al. found that D-myo-inositol-1,2,6-triphosphate blocked Cd induced hypertension in animals that were no longer being given Cd but clearly still had Cd in their tissues [76]. The increase in intracellular calcium from hydrolysis of phosphatidylinositol requires the phosphate to be at the 4,5 position [39]. In addition to acting as a chelating agent, it may block the action of Cd on the receptor responsible for increasing intracellular calcium.

Based on individual need, patients may respond to anti-fungal medications or replacement therapy with endocrine hormones.

Scientific Proof

A typical proof in toxicology would involve demonstrating that a toxic agent in blood, urine, or hair was correlated to a certain effect. In epidemiologic studies exposure to the agent in air, water, or food would be studied looking for a dose response effect. Such proofs are not helpful in detecting low dose Cd toxicity. Instead it is necessary to look for factors which would increase or decrease the effects of free Cd. These effects include genetic factors, nutritional effects, psychosocial stress, environmental chemical exposures, biologic exposures to viruses, fungi, and bacteria. There are so many variables that one comes face to face with the reality that all individuals are unique. Although many can suffer from the same symptoms the cause and most effective therapy of these symptoms may differ greatly.

By suspecting that Cd plays a catalytic role, it may be possible for research centers to gather more precise information on vitamin levels, platelet reactivity, beta-2 microglobulins, genotypes, and changes in ultrastructure of muscles and connective tissue. However, even the careful delineation of the pathophysiology of the disease process would not lead to a "magic bullet therapy." Cd is an essential element in a variety of cell processes. Decreasing free Cd to an adaptive level requires a multi-faceted approach and active participation by the patient.

The US budget for research is low considering the cost of health care. Since expensive large controlled trails are not an adequate way of detecting Cd toxic effects or finding the most appropriate treatment, it makes sense to consider innovative approaches. A large national computer that could accept input from physicians around the country regarding initial conditions of patients, responses to a variety of therapeutic strategies, as well as long term sequelae, would provide much needed information to the practitioner.

Table 1.

Protective Strategies

1. Clean air, no cigarette smoke
2. Clean water, no chloroform
3. Unprocessed food: fresh fruit and vegetables, cooked vegetables, cereals, nuts, seeds, yogurt, fish
4. Distress reduction
    - Controlled stress through gradually increased exercise
    - Increased self-esteem
    - Conflict resolution
5. Endogenous opiates
    - Stretching
    - Breathing
    - Exercise
    - Reflex stimulation
6. Nutritional supplements based on individual need
    - Ca, Mg, Zn, K, Fe, Cu, Se, Cr, I, Ge
    - Vitamin C to bowel tolerance, beta-carotene
    - Vitamin E, D, K
    - B-complex
    - Soy lecithin
    - Essential FA, omega 6 and omega 3
    - Bioflavonoids
    - Amino acids, cysteine, taurine, methionine, carnitine, lysine, histidine, arginine, ornithine, etc.
7. Hormonal replacement if needed
8. Anti-infective herbal remedies such as garlic, ecchinacea, rhizinate, or selected pharmaceuticals

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Biographical Sketch

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