Kawasaki`s Disease, Acrodynia, and Mercury

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Abstract: A superantigen or autoimmunity has been hypothesized to be the main cause of the Kawasaki`s Disease but the etiology is unknown. Medical literature, epidemiological findings, and some case reports have suggested that mercury may play a pathogenic role. Several patients with Kawasaki`s Disease have presented with elevated urine mercury levels compared to matched controls. Most symptoms and diagnostic criteria which are seen in children with acrodynia, known to be caused by mercury, are similar to those seen in Kawasaki´s Disease. Genetic depletion of glutathione S-transferase , a susceptibility marker for Kawasaki´s Disease, is known to be also a risk factor for acrodynia and may also increase susceptibility to mercury . Coinciding with the largest increase (1985-1990) of thimerosal (49.6% ethyl mercury) in vaccines, routinely given to infants in the U.S. by 6 months of age (from 75µg to 187.5µg), the rates of Kawasaki´s Disease increased ten times, and, later (1985-1997), by 20 times. Since 1990 88 cases of patients developing Kawasaki´s Disease some days after vaccination have been reported to the Centers of Disease Control (CDC) including 19% manifesting symptoms the same day. The presented pathogenetic model may lead to new preventive- and therapeutic strategies for Kawasaki´s disease.

Keywords: Kawasaki's disease, mercury, acrodynia, thimerosal, ethyl mercury, methyl mercury, vaccine, dental amalgam.

INTRODUCTION

Kawaski's Disease (KD), first described in Japan (1967), is an acute febrile multiorgan vasculitis, which predominantly (75 – 80%) affects children younger than 5 years. The disease has an increasing frequency and, in developed countries, has surpassed rheumatic fever as the leading cause of acquired heart disease in children. Early intravenous immunoglobulins in combination with acetyl-salicylic acid have significantly reduced the prevalence of coronary artery abnormalities.

There is no test for diagnosing KD; thus the diagnosis is based on clinical signs and symptoms. Despite of this, of all cases atypical ones amount to 10-45%. Interestingly, another childhood disease, acrodynia (AD) shares most of its diagnostic criteria with KD.

By now, the cause of KD is unknown. Antigens from infections as well as superantigens and genetic polymorphisms have been implicated in the etiological hypotheses. In this review of the literature and analysis of the U.S. Vaccine Adverse Effects Reporting System (VAERS), we hypothesize that prenatal and postnatal exposure to mercury (and synergistic toxins) may be a pathogenic factor in KD.

The VAERS database is an epidemiological database that has been maintained by the Centers for Disease Control (CDC) since 1990 as a surveillance tool to evaluate vaccine safety. An examination of the VAERS database (online public access version: http://vaers.hhs.gov/scripts/data.cfm) with reports entered through January, 31, 2008 was undertaken. The keywords: "kawasaki's disease" and "kawasaki's syndrome." were used. An additional search for "mucocutaneous lymph node syndrome" did not yield any results. The strength of the VAERS database stems from its large reporting base. Its potential weakness is that all vaccine-associated adverse events experienced are not reported.

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ACRODYNIA, KAWASAKI`S DISEASE AND MERCURY

AD was considered a mysterious, systemic disorder, mainly affecting children under the age of five. At its epidemic height (1880-1950), it affected about one in 500 children in industrialized nations [1].

The onset of AD is characterized by high fever lasting more than 5 days; a varying rash such as erythematous plaques, or appearing as measles or scarlet fever; swollen lymph nodes, particularly in the neck; bright red, swollen hands and feet; red, irritated eyes without discharge; bright red, irritated mouth, lips, and throat [2,3]. Neurological, cutaneous, and cardiovascular symptoms are most commonly seen. However, the disease is highly variable; cutaneous symptoms may be mild or lacking while neurological symptoms always seem to be present. It was explained as an infection or nutritional deficiency and it occurred mostly in the teething period [4].

In 1953, as a result of work by Warkany and Hubbard, mercury – coming from teething powders, baby powders, and diapers treated with calomel (85% mercurous chloride) [2] - was accepted as the cause of AD [2]. After a federal ban of these mercury-containing products in 1954, AD disappeared [1]. It should be noted that, *in vitro*, mercurous chloride is one of the least toxic forms of mercury, about 100 times less toxic than are mercury vapor or ethyl mercury contained in vaccines [5]. In addition, it was reported that applications of vaccines (containing ethyl mercury in thimerosal) preceded the onset of AD in several cases [2,3].

KD shares its diagnostic criteria with those of the onset of AD; the two diseases are similar in their clinical appearance. More than 150 symptoms and about 50 laboratory findings which are seen in KD were also described in cases with mercury poisoning (MP), too. (See Table **1**) [2,3,6-57]. KD affects males twice as often as females. This may be explained by *in vitro* studies on human cells which have shown that testosterone synergistically increases the toxicity of mercury, while estrogen protects against mercury toxicity [1].

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Table 1. Symptoms Shared Between Kawasaki's Disease and Mercury Poisoning [2,3,5-56]

Kawasaki's Disease	**Mercury Poisoning**
Diagnostic Criteria	**Typical Onset**
Persistent high fever lasting >5 days	Persistent high fever lasting >5 days
Varying rash such as erythematous plaques, or appearing as measles, scarlet fever	Polymorphous exanthema such as erythematous plaques, morbilliform, scarlatiniform
Swollen lymph nodes, particularly in the neck	Adenopathy, particularly cervical adenopathy
Bright red, swollen hands, feet	Erythema, edema of the hands, feet
Red, irritated eyes without discharge	Bilateral conjunctivitis without discharge
Bright red, irritated mouth, lips, throat	Stomatitis, erythema of the lips, pharyngitis
Mucocutaneous	**Mucocutaneous**
Peeling of the hands, feet, nose, genitals	Desquamation of the hands, feet, nose, genitals
Bright red, swollen cheeks, nose, genitals	Erythema, edema of the cheeks, nose, genitals
Bright red tongue with fungiform papillae	Erythema of the tongue with blisters
Lesions, ulcers of the mouth	Oral lesions, ulcers
Dry, cracked lips	Fissured lips
Jaundice	Icterus
Inflammation of the skin	Dermatitis
Small, pink drops on the skin	Guttate psoriasis
Painful, itching, burning sensations	Painful, itching, burning sensations
Poor circulation to the fingers, toes, and other extremities, causing discoloration	Raynaud's Syndrome
Beau's lines, pale nails	Beau's lines, pale nails
Cardiovascular	**Cardiovascular**
Rapid heart beat	Tachycardia
Irregular heart beat	Cardiac arrhythmia
Elevated or abnormally low blood pressure	Hypertension, hypotension
Inflammation of the heart muscle, heart valve, pericardium, coronary arteries	Myocarditis, valvulitis, pericarditis, coronary arteritis
Inflammation of the arterial walls, causing a thickening, hardening, loss of elasticity	Arteriosclerosis, atherosclerosis
Coronary artery lesions	Coronary arterial lesions
Abnormal fluid accumulation around the heart	Pericardial effusion
Inflammation, narrowing of the blood vessels	Stenosis
Blood clot	Thrombosis
Reduced blood supply to the heart	Myocardial ischemia
Enlargement of the blood vessels	Arterial ectasia
Enlarged heart	Cardiomyopathy, cardiomegaly
Coronary aneurysms, abnormalities	Coronary aneurysms, abnormalities
Heart attack, cardiac failure	Myocardial infarction, congestive cardiac failure
Respiratory	**Respiratory**
Asthma	Asthma
Chest paint	Angina
Difficulty breathing, shortness of breath	Dyspnea
Inflammation of the nasal sinuses	Sinusitis

(Table 1). Contd…..

Inflammation of the bronchi, lungs	Bronchitis, pneumonitis
Blood clot in the lung	Pulmonary embolism
Swelling, fluid accumulation in the lungs	Pulmonary edema
Interstitial thickening surrounding the bronchi	Peribronchial cuffing
Abnormal tissue changes in the lungs	Pulmonary nodules
Abnormal fluid accumulation around the lungs	Pleural effusion
Collapse of part or the entire lung	Atelectasis, emphysema
Respiratory tract infection	Respiratory tract infection
Neurological	**Neurological**
Marked personality change, severe irritability	Marked personality change, severe irritability
Chronic fatigue, weakness	Lethargy, asthenia
General feeling of discomfort, unease	Malaise
Headache, migraine	Headache, migraine
Coma, stroke	Coma, stroke
Convulsions, seizure	Convulsions, seizure
Hearing loss, ringing of the ears	Sensorineural hearing loss, tinnitus
Inflammation of the brain, meninges	Encephalitis, meningitis, meningoencephalitis
Incoordination	Ataxia
Facial paralysis	Bell's palsy
Musculoskeletal	**Musculoskeletal**
Swollen joints, joint pain	Arthritis, arthralgia
Muscle pain	Myalgia
Inflammation of the muscles	Myositis
Lower back pain, inflammation of the sacroiliac joint	Sacroiliitis
Abnormally low muscle tone	Hypotonia
Ocular	**Ocular**
Drooping eyes	Ptosis
Sensitivity to light	Photophobia
Inflammation of the uvea	Uveitis
Blurred vision, visual disturbances	Blurred vision, visual disturbances
Immunological	**Immunological**
Allergies, including nasal and eye allergies	Allergies, allergic rhinitis, allergic conjunctivitis
Increased susceptibility to disease, infection	Immunotoxic
Gastrointestinal	**Gastrointestinal**
Loss of appetite, poor appetite weight loss	Anorexia, poor appetite, weight loss
Nausea, vomiting	Nausea, vomiting
Diarrhea, constipation	Diarrhea, ileus
Bowel obstruction	Colonic obstruction
Ulcers, inflammation of the colon	Colitis ulcerosa
Inflammation of the bile ducts	Cholangitis
Enlarged liver	Hepatomegaly
Kidney failure, nephritic syndrome	Renal failure, nephrosis

Probably, cases with symptoms similar to KD were designated as Feer disease or AD before the discovery of KD [6]. One case of AD mimicked KD and was induced through inhalation of mercury vapor [7]. In another report, published in 2004, two brothers (3 and 20 months of age) presented with similar symptoms and were first diagnosed as having KD. Laboratory testing revealed that both had elevated urinary mercury levels, so a diagnosis of AD was made [8].

Mercury's possible role in KD was first suggested by Donald Cheek (Australia, 1975) after he noticed clinical similarities to AD [56]. In addition, Orlowski and Mercer found mercury levels in the urine of six patients with KD elevated, compared to controls. One patient was treated successfully through mercury detoxification with D-Penicillamine [58].

POSSIBLE SOURCES OF HUMAN MERCURY EXPOSURE

According to the U.S. Environmental Protection Agency (EPA) and the National Academy of Science, about 8-10% of American women have mercury levels sufficiently high to cause neurological disorders in most of their children [1]. Numerous studies have suggested that maternal dental amalgam is one of the main sources of prenatal mercury exposure [58,99]. Dental amalgam fillings contain at least 50% elemental mercury, which is continuously emitted as mercury vapor and is easily absorbed by human tissues. Mercury vapor is acknowledged as one of the most toxic forms of mercury, as it penetrates into the cells with great ease, which is not possible for inorganic forms of mercury. Other prenatal sources of mercury include vaccines, immune globulin, and fish. Postnatal sources of mercury include thimerosal from vaccines and mercury from breast milk. During childhood, dental amalgam fillings and, especially in populations with great fish consumption, fish are the main sources of mercury. According to the pharmaceutical company Eli Lilly, the inventor and producer of thimerosal since 1928, this ethyl mercury antiseptic may cause severe mental and motor retardation in children and the unborn [59]. Thimerosal is the form of mercury particularly capable of inducing cutaneous symptoms and diseases, such as those seen in KD [1,9].

The US Food and Drug Administration (FDA) compiled a list of medical products still containing mercury (See Table **2**) [62]. Several medical tests, too, may expose a patient to thimerosal, such as those for hepatitis or strep [63].

While some experiments have shown that methyl-mercury-jodide or methyl-mercury-chloride, commonly used in experiments, may be more toxic than ethyl-mercury, still exposure to the form of methyl-mercury found in fish may be less toxic, possibly because it has already reacted in fish tissues and is tightly bound to sulfur groups or selenium [1,61]. Also, mercury vapor (e.g., from dental amalgam) seems to have even stronger toxic effects to the offspring of animals than does methyl-mercury-chloride [62].

GENETIC SUSCEPTIBILITIES OR SENSITIVITIES

Mercury toxicity is primarily retention toxicity, and its adverse effects depend largely on how much is retained in cells and tissues as opposed to being excreted. After a given quantity of intake, high urine mercury levels tend to be a sign of healthy excretion, while low levels tend to indicate an inability to effectively excrete mercury. This may be influenced by genetic susceptibilities or synergistic toxins, which increase the retention and, thereby, the toxicity of mercury [1,85].

According to a recent study of 67 Korean children with KD and 252 healthy controls, genetic depletion of glutathione S-transferase (GST) may be a susceptibility factor for KD. The frequency of the doubly deleted genotype (-/-) of GSTM1 and GSTT1 was found to be significantly elevated compared to the intact genotype (+/+) in KD patients [99].

Table 2. Past and Current Sources of Mercury Exposure [63-64,149-163]

Primary	Laxatives	**Foods (non-fish)**
Amalgams	Medical tests	**Mercury spills**
Vaccines	Nasal sprays	**Occupational exposures**
Fish	Ointments	Dentistry
Other	Oral supplements	Industry
Barometers	Plasma infusions	Mining
Batteries	Talcum powders	**Paints**
Biologicals	Topical sprays	Tattoo inks
Anthelmintics	**Root canals**	**Pesticides**
Antifungals	**Chemical solvents**	**Pollution**
Antiseptics	Bleach	Krematories
Baby powders	**Cosmetics**	Chlorine chemical plants
Diapers (treated)	Creams	Coal-fired power plants
Ear drops, antibiotics	Mascaras	Proximity to industry
Eye drops, antibiotics	Skin-lightning creams	
Hemorrhoid applications	**Drinking water**	
Immune globulins	**Fluorescent lightings**	
	Thermometers	

Genetic depletion of GST may be a susceptibility factor for autism [95,96] and AD. It increases susceptibility to xenobiotics like mercury, too [102-104]. In a study of 192 adult Austrian students, those with the doubly deleted genotype of GSTM1 and GSTT1 were found to have significantly increased hair mercury levels compared to those with the intact genotype [105]. The authors concluded that double deleted genotype of GSTM1 and GSTT1 increase the retention of mercury. This observation is in contrast to the results of Holmes and Coauthors who found decreased mercury levels in the hair of autistic children despite of their higher prenatal mercury exposure [105].

This was interpreted by assuming that autistic children's capacity to excrete mercury is reduced. But they used babies' first hair cuts while hair analysis of much older individuals with assumed reduced mercury excretion capacity have shown higher mercury levels in blood or hair [107,108].

Thus, it seems possible that individuals with deleted genotypes of mercury detoxifying enzymes - like those of the GST-family - are more likely to accumulate mercury during their growth periods than are individuals without genetic polymorphism. Thus, a critical level may be reached in body tissues and, because of possible osmotic balancing between extracellular and intracellular mercury, hair mercury levels may increase and finally tended to be higher.

In addition, mercury reduces the amount of reduced glutathione (GSH) available in the body [1,85,114]. GSH is necessary to detoxify heavy metals such as mercury from cells, neurons, and the liver [1].

Beside the toxic effects, mercury may also affect the immune system. In this context, it is important to note that KD was also regarded as an autoimmune disease or hypersensitivity to mercury. Mercury binds tightly to, e.g., sulfhydryl groups in tissues, thus altering the molecular structure. T-lymphocytes mistakenly recognize metal-modified cells as foreign and may start an autoimmune process [109, 145]

The possible Type IV-sensitation to thimerosal or mercury is testable by a specialized Lymphozyte transformation test, the Memory Lymphocyte Immuno Stimulation Assay (LTT-MELISA), especially adapted for this purpose [111]. It was shown in several reports that Type IV-immune reactivity against mercury was normalized after safe removal of dental amalgam fillings which was also accompanied by health improvement in patients with autoimmune diseases [110-113].

We recommend to use the LTT-MELISA test in any evaluation of possible side-effect due to mercury exposure. This test is not only a valid indicator of mercury allergy, but, in addition, it may provide important information about the source of sensitization, since inorganic mercury and thimerosal do not cross-react immunologically [111], It is noteworthy, that, following amalgam removal, the health of the majority of patients improved together with the decreased specific lymphocyte proliferation *in vitro* [112].

KD AFTER VACCINATIONS

In one case, a 35-day old male developed KD the day after receiving a second dose of Hepatitis B-vaccine (HepB), known to contain thimerosal. An association between HepB vaccination and vasculitis has also been reported in adults [65]. Thimerosal seems a likely mediator of that association since mercury is known to cause inflammation of blood vessels [23].

According to the VAERS data, several vaccines may have caused a number of cases of KD after vaccination, mostly Hemophilus B conjugate (HiB), Heptavalent pneumococcal conjugate (PNC), Diphteria and tetanus toxoids and pertussis (DPT), Measles mumps rubella virus (MMR), Diphteria and tetanus toxoids, pertussis vaccines absorbed. Hepatitis B conjugate., and inactivated poliovirus (DTA-PHE), Inactivated poliovirus (IPV), and Hepatitis B virus (HepB) vaccines. Some of them are known to still contain thimerosal, a few to have contained it before the reduction in the US (1999 – 2004) was made (See Table **3**) [66-71].

Altogether, we counted 88 patients (with an average age of 17 months) developing KD around 10 days after vaccination who were reported to the CDC since 1990.

ETHYL MERCURY IN VACCINES AND THE PREVALENCE OF KD

In the U.S., a rising trend in the incidence of KD was noted 1986-1997[72-74], with the highest increase 1986-1990 (See Table **4**) [72]. The largest increase corresponds exactly to the period when the federally mandated vaccine program was implemented, which substantially increased vaccine coverage and thus mercury exposure.

According to the CDC, states rarely reject a routine vaccination on schedule. Prior to the program, most states did not vaccinate as much, and several did not routinely vaccinate. The program forced millions of infants and children into routine vaccinations using vaccines which mostly contained thimerosal. For children 0-2 years of age, the number

Table 3. Current US Vaccines with the Ethyl Mercury Preservative Thimerosal [66-71]

Routine (0-6 years of age)	Non-routine (all ages)
***DPT –** Diptheria-Pertussis-Tetanus	**BCG** – Bacillus Calmette-Guérin (tuberculosis)
Flu – Influenza	**DT** – Diptheria-Tetanus toxoids
***HepB –** Hepatitis B	**JE** – Japanese encephalitis
***Hib** – Haemophilus influenzae type B	**MNC** – Meningococcal conjugate (meningitis)
	RAB – Rabies
	TD – Tetanus-Diptheria toxoids
***Reduced between 1999-2004**	**TT** – Tetanus toxoid

Table 4. Incidence of Kawasaki's Disease in the US [72-74]

Year	Cases per year	+/-	Children affected <5 years	+/-
1976-1985	213	-	1.1 in 100,000	-
1984-1990	1,960 (+1,747)	+820.2%	9.2 in 100,000	+736.4%
1988-1997	3,009 (+ 1,049)	+53.5%	13.6 in 100,000	+47.8%
1997	4,525 (+1,516)	+50.4%	18.1 in 100,000	+33.1%
2000	4,248 (–277)	-6.1%	17.1 in 100,000	-5.5%

Table 5. Cumulative Mercury Exposure from Routine US Childhood Vaccines by 6 Months of Age [66-71]

Year	Cumulative exposure	+/-	Vaccines with thimerosal	+/-
1928-1973	25-50µg	-	1-2 DPT	-
1973-1986	75µg (+37.5µg)	+100%	3 DPT	+100%
1986-1990	150µg (+75µg)	+100%	3 DPT + 3 Hib	+100%
1990-1999	187.5µg (+37.5µg)	+25%	4 DPT + 3 Hib + 3 HepB	+66.7%
2004-2007	90.6µg (-96.6µg)	-51.7%	4 DPT* + 2 Flu + 3 Hib + 4 HepB*	+30%

*Trace amounts (<5µg) of thimerosal.

of routine vaccines on schedule more than tripled from 10 to 36 doses between 1983 and 2007, while coverage increased from 60 to 84% between 1985 and 1995 [75].

Moreover, the HiB vaccine was added to the schedule in 1986. This increased the amount of thimerosal infants by 6 months of age were exposed to, from 75µg to 150µg - the largest increase of mercury intake from routine childhood vaccinations. After addition of the HepB vaccine in 1990, US children were cumulatively exposed to 187.5µg of thimerosal by six months of age (See Table **5**) [70,71]. However, this does not take into account non-routine childhood vaccines such as influenza and tetanus, which contain about 25µg of thimerosal in a single dose (See Table **3**) [66-69]. An average cumulative thimerosal exposure to 62.5µg thimerosal from 3 vaccines would leave a healthy infant with mercury values 100 times higher than that which the EPA considers safe (0.1µg mercury/1kg bodyweight per day) [76].

After a substantial increase in infants' exposure to mercury from routine vaccinations, KD immediately rose tenfold over a period of five years (1985-1990). By 1997, KD had increased 20-fold from its initial figure in 1985. Prior to this epidemic increase, the incidence of KD had remained at a fairly low, constant rate for over a decade after the first US case had been recognized in 1975 [72-74].

Following the reduction of mercury in US vaccines beginning in 1999 (See Table **6**), a 6.1% drop was seen in KD incidence rates [72-74]. However, thimerosal is still being used in several children's vaccines, including the influenza vaccine which has recently become routine and multidose HiB vaccines. Pregnant women, too, are being vaccinated far more frequently in recent years, particularly for influenza [77].

Countries with vaccination programs similar to the one in the US, but with lesser thimerosal, experience a significantly lower incidence of KD. Denmark and Germany, having reduced thimerosal in the early 1990s, currently have KD rates of 5 and 9 per 100,000 people, respectively, - less than half the rate in the US.

SEASONALITY OF KD AND SUDDEN INFANT DEATH SYNDROME IN RELATION TO THE FLU VACCINE

In the US, Winter-Spring seasonality is seen in KD, with highest incidence between October and March [73,74]. Recently, local outbreaks have become far more common during these same months in the US [74]. A similar seasonality is seen in Sudden Infant Death Syndrome (SIDS) for infants 1-4 months of age during Winter [93]. In Japan, KD follows a similar Winter-Spring seasonality [78].

Table 6. Mercury in Routine US Childhood Vaccines (0-2, 0-6 years) and all Vaccines [66-71]

Year	Childhood vaccines	%	All vaccines	%
<1999	-	>50%	-	>50%
1999	13 out of 28	46.4%	-	-
2004-2007	3 out of 30, 5 out of 20	10%, 25%	13 out of 34, 16 out of 42	38.2%

Source: CDC, FDA.

Beside the higher incidence of vitamin D deficiency, which causes or boosts many diseases [79]; this seasonality may be explained by increased thimerosal exposure from flu shots during Fall and Winter months. Based on CDC data for the 2004-2005 flu season, the vaccination rate for influenza was 48.4% for US children aged 6-23 months [81]. Yearly influenza inoculation with two doses has become standard.

METHYL MERCURY IN FISH IN RELATION TO KD AND MINAMATA DISEASE (MD)

KD affects Asians more than any other ethnic group. First, it appeared in Japan, where the incidence rates are highest (135 cases per 100,000 children under five years). As regards the U.S., KD was first reported in Hawaii which currently has the largest incidence of 48 in 100,000 for children under five years, or 125 in 100.000 among those of Japanese descent) [74]. Mercury levels in the environment and in fish have been increasing over the last decades. High methyl mercury intake from fish and seafood may explain why Asians are roughly 6-10 times more likely to contract KD than Caucasians [11,12].

Like KD and AD, MD appeared as a previously unknown neurological disorder in Japan in 1956. It shares many symptoms with KD. It was during the height of MD outbreaks and heavy mercury pollution, 1956-1968, that, five years after MD, KD was first diagnosed in Japan. The temporal and geographical coincidence of KD, MD, and the mercury contamination at Minamata Bay is noteworthy. In 1959, it was found that MD was caused by industrial mercury wastes dumped into Minamata Bay, which was transformed into organic methyl mercury after bioaccumulating in the local fish and seafood [82].

It is remarkable that both AD and MD were long suspected to be caused by infectious agents, until mercury was established as causal several years or decades later. It seems unlikely that KD is caused by an infectious agent, since it is not contagious. KD also has a reccurrence rate of 1% to 5%, while reccurrences of infectious diseases are very rare [11].

KD AND IDEOPATHIC DILATED CARDIOMYOPATHY

Idiopathic Dilated Cardiomyopathy (IDCM) is characterized by sudden or progressive cardiac failure, resulting from the dilation of one or both of the heart ventricles.

In multi-element analyses of heart biopsies, only mercury and antimony were found to be 22,000 and 12,000 times, respectively, higher in hearts than in control tissues. in IDCM patients compared to controls [83]. Antimony may be a contaminant of dental amalgams [164].

Atypical cases of KD, which are 5 times more likely to exhibit cardiovascular problems than are typical KD sufferers, may look somewhat similar clinically to IDCM. Atypical cases occur more frequently in patients over eight years of age, shortly after the first amalgam fillings are usually placed [87]. The mortality rate for KD is 13 times higher for patients above 10 years of age (1.4%) than for those below 10 (0.11%).

For further research purposes, the tissues, particularly the heart, of KD patients should be examined for mercury content, if the patient died as a result of cardiac failure. In addition, oral status regarding the presence of amalgam fillings should be examined as well.

DIAGNOSING MERCURY POISONING MP AND TREATMENT

According to the World Health Organization (WHO), there is no correlation between mercury levels in blood or urine and critical organs such as brain and kidney [86]. For mercury exposure from dental amalgam or ethyl mercury, it was found that mercury levels in biomarkers such as urine, blood, or hair did not correlate with mercury levels in body tissues [85,94]. Also, no correlation with mercury levels is seen for either number or severity of symptoms, and even at the same level of exposure, patients range from being severely affected to appearing aymptomatic [2].

Therefore, there exists no objective diagnostic test for the estimation of mercury body burden in living subjects. Some authors have suggested that mercury excretion after the application of a mercury chelating agent may be a better tool for the diagnosis of mercury toxicity [146]. Chelation therapy is used to provoke the excretion of heavy metals such as mercury, and has been successfully employed to substantially improve or cure MP [8,9,13,23,147]. Improvement of one patient with KD after mercury chelation was also reported [58].

However, severe or long-term exposure to mercury may cause irreversible damage, particularly in a unborn or even developing child. The effectiveness of chelators in this situation is not entirely clear and is currently under debate, although successes have been reported [89,90].

2,3-dimercaptopropanol (BAL) and D-penicillamine were preferred in the treatment of mercury poisoning until recently, due to safety concerns. Safer and more effective chelators have since replaced them, such as meso-2,3-dimercaptosuccinic acid (DMSA) and 2,3-dimercapto-1-propanesulfonic acid (DMPS). While several case reports and animal studies have confirmed the safety and effectiveness of these chelators, only DMSA taken orally has been approved by the FDA specifically for treating MP [89-93].

The patient's overall condition after chelation tends to be the most reliable indicator of MP, followed by urine mercury levels. Patients suffering from AD may exhibit low or normal urinary mercury excretions compared to controls, and only display mild increase of urine mercury levels after chelation. Therefore, patients suffering from idiopathic symptoms relatable to MP should be further evaluated [96]. Additionally, as described above, the LTT-MELISA is recommended for evaluation of possible side-effects of mercury exposure [148].

SYNERGISTIC TOXICITY

Synergistic effects of mercury with other heavy metals such as aluminum, lead, and cadmium was suggested. Schubert *et al*. found that when the letal dosis of lead that kills 1% of the test animals ($LD1_{Pb}$) was combined with the LD1

Table 7. Current US Vaccines for all Ages [66,67]

Routine	Mercury		Aluminum*		Antifreeze		Formaldehyde*		Phenol		Antibiotics*	
Varicella											+	
Vaccinia									+		+	
Typhoid									+			
TT		+										
TD		+		+				+				
RAB		+		+						+		+
PNC				+						+		
Non-routine												
MNC		+										
MMR												+
JE		+						+				
IPV		–		+		+		+		+		+
HIB		+		+				+				
HEPB		–		+		+		+		+		+
HepA				+		+		+		+		
FLU		+				+		+		+		+
DT		+		+				+				
DPT		–		+		+		+		+		+
BCG		+										
Anthrax		+				+						

*Synergistic toxicity with mercury.
+Full amount–Trace amount.

of mercury, all of the animals die ($LD1_{Pb} + LD1_{Hg} = LD100$) [119].

Beyond thimomersal, vaccines contain several other chemical additives, many of which are known toxins or carcinogens (See Table **7**) [66,67]. Some, like aluminum and formaldehyde, and neomycin, may be synergistic with mercury [1], while others, such as phenol, may produce symptoms seen in KD [120]. Formaldehyde is routinely used in vaccines as a preservative [121]. Antifreeze, or ethylene glycol, is a agent used in vaccines as an antiseptic [122].

Antibiotics, if given often to infants, may increase the retention of mercury [123]. This is not easy to explain, because some antibiotics contain sulfhydryl groups, which, on the contrary, may protect from mercury toxicity. Also, Penicilline is transformed into Penicillamine in the body, which is a known mercury chelator. But others have suggested that antibiotics also reduces the gut microflora which may increase the total absorption of mercury [124].

Infants are unable to effectively excrete mercury through the biliary transport system, as a result of not producing adequate amounts of bile in the first few years of life [1]. Infants also lack a fully developed central nervous system and blood brain barrier, which leave them to be more susceptible to mercury exposure [126].

CONCLUSION

Published data suggest that mercury in all chemical forms may play a pathogenic role in KD. We suggest that further studies be conducted, and that physicians evaluate their KD patients for MP. Potential sources of exposure should be closely examined. It is important to note that a silent latency period between the time of exposure and observable symptoms may be seen in AD, particularly with chronic low-level exposure [128].

For further research, a comparison of mercury exposed patients vs. non-exposed ones should be conducted, since comparing healthy and unhealthy persons, both exposed to mercury, can lead to false conclusions when individual detoxification capacities are disregarded. Further research should be done to evaluating the potential therapeutic effects of mercury chelation in KD. It is important to note that, for mercury, a safe level of exposure has never been established [86]. Given the historical precedent for low-level exposures from one of the least toxic forms of mercury to cause the childhood epidemic of AD, we urge for a preventive reduction of the use of mercury both medically and commercially.

LIST OF ABBREVIATIONS

AD = Acrodynia

BAL = 2,3-mercaptopropanolol

BCG = Bacillus Calmette Guerin (tuberculosis)

CDC = Centers for Disease Control

DMPS = 2,3-dimercapto-propane-sulfonic acid

DMSA = meso-2,3-dimercapto-succinic acid

DPT = Diphteria pertussis tetanus

DT = Diphteria and tetanus toxoids

DTAPHE = Diphteria and tetanus toxoids, pertussis vaccines absorbed. Hepatitis B conjugate, and inactivated poliovirus

DTP = Diphteria and tetanus toxoids and pertussis

EPA = Environmental Protection Agency

FDA = Food and Drug Administration

FLU = Influenza

GSH = Reduced Gluthation

GST = Gluthation S-Transferase

HepA = Hepatitis A virus vaccines

HepB = Hepatitis B virus vaccines

HiB = Hemophilus B conjugate

IDCM = Idiopathic Dilated Cardiac Myopathy

JE = Japanese encephalitis

IPV = Inactivated poliovirus

KD = Kawasaki's disease

LD = lethal dose

LTT = Lymphocyte Transformation Test

MD = Minamata Disease

MELISA = Memory Lymphocyte Immuno Stimulation Assay

MMR = Measles mumps rubella virus

MNC = Meningococcal conjugate (meningitis)

MP = Mercury poisoning

PNC = Heptavalent pneumococcal conjugate

RAB = Rabies

TD = Tetanus diphtheria toxoids

TT = Tetanus toxoids

SIDS = Sudden Infant Death Syndrome

VAERS = Vaccine Adverse Effects Reporting System

WHO = World Health Organization

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