The effect of mercury on the brain and general health

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The role of metals in human diseases is currently a hot research topic worldwide. Abnormal deposition of iron in the brain of patients suffering from neurodegenerative diseases such as Parkinson's, Alzheimer's and multiple sclerosis has been firmly established. It is less known that exposure to mercury and other metals may result in disturbance of the brain iron transport and cause abnormal iron deposition.

Depression is a risk factor of many debilitating diseases such as the neurologic diseases mentioned above, but also in cardiovascular disease and allergic diseases. The common factor of these diseases is inflammation, and there is a connection with depression and inflammation in the body (Dantzer 2008). This causal relationship was first described 20 years ago and only now it starts to receive attention (MacDonald 1987). After activation, inflammatory cells release so called cytokines which affect the brain through deregulation of hypothalamic-pituitary-adrenal axis (HPA). This system is a part of the neuroendocrine system that controls vital functions such digestion, the immune system, energy usage, but also mood reaction to stress. Thus, deregulation leads to multi-symptoms such as profound fatigue, fibromyalgia, psychosomatic problems and sleep disturbances among others (Turnbull 1995). As summarised by Maes, psychological stress might not only cause immune activation, but it might also result in immunosuppression (Maes 1999).

Current medicine treats the inflammation underlying the diseases, but does not look for the cause of the inflammation. Recognized causes of inflammation are bacteria and viruses. Metals are often overlooked since metal-induced inflammation (allergy) is usually regarded only as skin disease or oral problem and not as systemic disease. In addition, metals cause inflammation only in some individuals, and not in all exposed subjects. Allergy to metals is mainly measured by patch/skin testing which measures cellular Type IV hypersensitivity. This means, that certain type of white blood cells - T-lymphocytes - are specifically stimulated by metals. Serum factors, so called antibodies, are absent. In contract to a Type I allergy, which is mediated by serum IgE antibodies, a Type IV allergic reaction is mediated by T memory cells, white blood cells

sensitized to given allergen previously. Following renewed exposure, memory lymphocytes will recognize the allergen and divide. The newly formed cells secrete cytokines and participate in the resulting allergic reaction. In patch testing, the suspected allergen is applied on the skin of the back under occlusion and redness and swelling 2-3 days later is taken as an evidence of positive response. Although a gold standard in dermatology, this test suffers from several disadvantages such as risk of sensitization by direct application of a toxin on the skin and low reproducibility of subjective reading.

A blood test, which can measure allergy to metals outside the body (*in vitro*) has been around since the 1960's. In the beginning, the test, a so called lymphocyte transformation test (LTT), was not standardized and therefore had low clinical relevance. In the 1990's however, two modifications of this test were developed, the beryllium LTT test and the LTT-MELISA® test which are now accepted methods to evaluate an allergy to metals (Newman 1996, Valentin-Thon 2003, 2006, Stejskal 2006). According to patch test results, inorganic mercury and thimerosal (an ethylmercury preservative in vaccines and pharmaceutical preparations) are the most frequent allergens in children together with nickel. In 1094 Italian children with skin disease, 10% reacted to thimerosal (ethyl mercury salt) and 6% to mercury (Seidenari 2005). In Spain, skin test reactivity to thimerosal was 21% and to mercury 19% (Vozmediano 2005). A high prevalence allergy to mercury was also found in LTT-MELISA® in patients with CFS-like syndrome (Stejskal et al.1999) and in patients with autoimmune disorders (Prochazkova et al. 2004) who improved following replacement of dental amalgam.

The danger of heavy and transition metals resides in their physicochemical properties; binding to sulfur and other groups in the mitochondria, enzymes and cell proteins. Fat-containing organs such as brain or collagen-containing structures are especially rich in SH-groups and therefore vulnerable to metal binding. Metals also induce free radical formation, inactivate enzyme and mitochondrial activity (Nuttal 2004).

The effect of high concentrations of metals on the brain and mental health has been thoroughly studied in occupationally exposed workers. It is established that metals such as mercury and lead are toxic to nerve cells. Acute intoxication with mercury leads to (amongst other symptoms) loss of appetite, weight and hair loss, severe hypertension and personality changes. Acute intoxication with mercury is fortunately infrequent and mainly affects specific professions as miners, or people living in polluted areas, for example through a factory's wastewater

.Diagnostic tests include blood testing, urinary excretion and hair analysis and are based on the excretion of toxic metals from the body. If a person is not excreting the metal due to for example a lack of detoxification enzymes, these tests can be misleading (Nuttal 2004).

Most people are exposed to low concentrations of metals on a daily basis and therefore it is surprising that researchers have not focused on how this affects health. Some metals, such as zinc and iron, are essential for human health, while many others, like mercury and lead, have no role in the human body. After the ban of leaded petrol, mercury released from dental amalgam is the biggest source of mercury for man according to WHO Environmental Health Criteria (WHO 1991). For this reason, this article will concentrate on the mercury issue despite of the fact that other metals such as lead, manganese and arsenic can cause neurotoxicity and other health problems as well (Wright 2007). In addition to dental amalgam, polluted fish is a source of methylmercury and cigarette smoke contains many metals such as mercury, cadmium, nickel, lead and arsenic. Some adult vaccines and pharmaceutical preparations such as eye drops still contain mercury-preservative-thimerosal.

Health authorities in the United Kingdom stand by their claim that amalgam fillings are absolutely safe and there exists no reasons to replace functioning fillings. That mercury has recently been banned in Norway and Sweden does not seem to matter. The argument is that the mercury released from fillings is below a “safe level” established in professional environment. A review of current scientific literature does show that a chronic, low dose exposure to metals, can cause health problems. Before discussing the specific studies reporting the connection between metals and mental health, it is important to mention a common misunderstanding when it comes to exposure to metals such as mercury: the importance to distinguish between toxic and immunologic effects of metals. Toxic effects occur at high levels, such in working or other accidents when a whole area is polluted, and are thankfully rather rare. Immunologic effects such as allergy or autoimmunity can occur only in susceptible genetically predisposed subjects, and in those cases even very small amounts of the offending substance is enough for development of ill-health.

Scientific literature is full of evidence of “mercury poisoned” people whose symptoms disappeared after removing their fillings (Wojcik 2006, Stejskal et al. 1999, Prochazkova and

Sterzl 2004). Since mercury is usually not regarded as allergen, it is not surprising the most of the dentists is not aware of the fact that even low concentrations of not only mercury as well as other dental metals (nickel, gold, palladium) might be harmful for allergic patient.

When approached, most dentists will reject patients' suspicion that mercury in amalgam fillings are making them sick, saying there is no proof, no laboratory tests showing that they are "poisoned". The problem is the term "poisoned". If patients would say that they are allergic to mercury, they would possibly be taken seriously. The British Dental Association estimates that 3% of the population suffers from mercury allergy. However, as it was stated in its policy to dentists in United Kingdom, this was considered a rare occurrence and the patients need not to be informed.

Below are some studies which illustrate the effects of metals on the brain.

Neuropsychiatric performances in workers occupationally exposed to mercury

The air at Ground Zero following September 11, 2001, was heavily polluted with metals and chemicals from the destroyed Twin Towers, and service personnel and residents of Lower Manhattan inhaled these particles for extended periods of time. A study on 160 subject found that most individuals had eight or more serious health complaints, including severe respiratory problems, digestive problems, skin rashes, sleeplessness, anxiety, depression, weight gains, elevated blood pressure, lethargy, and recurrent headaches. Heavy metal toxicity was suspected as a causal factor for many of these symptoms. Of those tested for heavy metal toxicity, using a challenge urine test, 85% had excessively high levels of lead and mercury. Patients were treated by chelation using dimercaptuosuccinic acid (DMSA). Chelators, from the Greek word "chelos", meaning claw, are substances which bind tightly to metals and remove them from the body. After three to four months of treatment, the first cohort of 100 individuals reported significant (greater than 60%) improvement in all symptoms (Kokayi 2006).

Another study looked at the neuropsychological performances of 26 ex-workers at a fluorescent lamp factory with chronic mercury poisoning. The workers had been exposed to mercury for an average of 10 years and had been away from this work for approximately 6 years. Twenty control subjects matched for age, gender and education were used for comparison. The neuropsychological performances of the former workers suggest that occupational exposure to

elemental mercury has long-term effects on information processing and psychomotor function, with increased depression and anxiety (Zachi 2007).

Further studies has shown miners exposed to mercury vapour during three years had intellectual damage, emotional changes (symptoms of depression and anxiety) and neurological changes (amnesia, insomnia and tremor of the tongue), as compared to miners who were not exposed to this vapour (Tirado 2003). Ex-miners also tend to be more introverted and sincere, more depressive, more rigid in expressing their emotions and are likely to have more negative self-concepts than controls (Kobal 2006).

Neuropsychiatric studies on effects of chronic effects of mercury released from dental amalgam.

Studies of the effects of low dose chronic effects of mercury released from amalgam fillings are less frequent than the epidemiologic studies of workers but show similar health outcomes. The occurrence of neuropsychiatric symptoms such as fatigue, insomnia, anxiety and anger in 25 women who had amalgam fillings was compared with 23 women without amalgams. The women with amalgams had significantly higher levels of mercury in the saliva and showed more symptoms of fatigue and insomnia. They experienced more intense angry feelings and were significantly less pleasant, satisfied, happy, secure, and steady, and had a more difficult time making decisions. The study suggests that mercury released from amalgam may be an etiological factor in depression, excessive anger, and anxiety, perhaps because mercury affects neurotransmitters in the brain (Siblerud 1994).

The same group of scientists studied the smoking habits of 119 subjects without amalgam fillings and compared them to 115 subjects with amalgams. The amalgam group had 2.5-times more smokers per group than the non-amalgam group, which was highly significant. Since mercury decreases dopamine, serotonin, norepinephrine, and acetylcholine in the brain, and nicotine has just the opposite effect on these neurotransmitters, this may help explain why persons with dental amalgams smoke more than persons without amalgams (Siblerud 1993).

Finally, the mental health status of 47 multiple sclerosis patients with amalgams was compared to that of 50 patients who had their fillings removed. Multiple sclerosis subjects with amalgams

suffered significantly more depression, hostility and psychotism, and were more obsessive-compulsive than the patients with removed fillings. These data suggested that the poorer mental health status exhibited by multiple sclerosis subjects with amalgam fillings may be associated with mercury toxicity from the amalgam (Siblerud 1992).

The beneficial effect of replacement of dental amalgam in patients suffering from various allergic and autoimmune diseases has been confirmed in more recent studies. (Prochazkova 2004, Sterzl 2006, Stejskal 2006, Valentin-Thon 2006).

Biochemical markers of mercury-susceptible populations

In a New Zealand study already mentioned above (Wojcik at al) 465 patients were diagnosed as having chronic mercury toxicity according to well-established criteria. Thirty-two percent of patients suffered from severe fatigue, 89% patients had memory loss, and 28% had depression. A significant correlation was found between a special variant of Apo-lipoprotein E gene and increased amalgam susceptibility, indicating that genetic factors may play role. Removal of amalgam mercury fillings combined with chelation and anti-oxidant treatment resulted in significant symptom reduction ($p<0.001$) to levels reported by healthy subjects. These data confirm previously published findings from the same group (Godfrey 2003) and of others regarding susceptibility to Alzheimer disease (Roses 1998) and to toxic effects of lead (Stewart 2002). Custodio and co-workers studied 309 gold miners and unexposed controls regarding mercury concentration in body fluids. The results indicated that a special variation of the gene involved in the synthesis of glutathione was present in individuals who had increased blood, plasma and urine levels of mercury. Since glutathione is used for detoxification of mercury and other metals, subjects with decreased glutathione availability might have problems with detoxicification of mercury (Custodio 2005).

Recently, clinical studies on the possible neurobehavioral effects of dental amalgam in children were reported, usually with negative outcome (Bellinger 2006). At the beginning of study, children previously diagnosed with psychological, behaviour, neurological or immunological disorders were eliminated from the studied group. One wonders if these children might have

been susceptible to amalgam and therefore the lack of the effects in healthy children does not exclude the effect in susceptible ones. Future studies should deal with the replacement of amalgam in susceptible subjects such as those with detoxification defects or allergy to mercury. Until now, the application of new scientific knowledge in clinical praxis has been slow and for many toxicants, their involvement in the origin on the diseases was known 20 years ago (Grandenjean 2008). Let's hope that with the new objective evidence available for the selection of susceptible groups, the scientific findings will be used in clinical praxis sooner.

Summary:

Mercury has strong toxic and allergenic properties. In addition to acute toxicity experienced in occupationally exposed workers, susceptible groups such as those with allergic predisposition and autoimmune disorders might be especially prone to low doses of mercury.

In subjects chronically exposed to low doses of mercury, testing for levels of metals in blood, urine or hair does not indicate ill-health. The susceptible individuals might have developed allergy to mercury and this can be determined at the Dermatology clinic by patch test or by blood test LTT-MELISA®. Genetic testing has not yet been used outside the occupational setting but seems to be a promising option in the future.

In allergic individuals, exposure to mercury or other toxic substances should be eliminated. Any removal of amalgam fillings has to be done by an informed dentist following maximal protection against mercury exposure. Non metallic dental materials should be used, such as composites and ceramics.

Detoxification and anti-oxidant treatment with minerals and vitamins counteracting the effect of mercury and other metals may be prescribed by a physician.

References:

Bellinger DC, Trachtenberg F, Barregard L, Tavares M, Cernichiari E et al. Neuropsychological and renal effects of dental amalgam in children. A randomized clinical trial JAMA 2006;295:1775-1783

Custodio HM, Harari R, Gerhardsson L, Skerfving S, Broberg K. Genetic influences on the retention of inorganic mercury. Arch Environ Occupat Health 2005; 60:17-23

Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;9:46-56

Godfrey M, Wojcik DP, Krone ChA. Apolipoprotein E genotyping as a potential biomarker for mercury neurotoxicity. J of Alzheimer Dis 2003;5:189-195

Grandjean Philippe. Late insights into early origins of disease. Basic & Clinical Pharmacology & Toxicology 2008;102:94–99

Kobal GD, Kobal AB, Arneric N, Horvat M, Zenko B et al. Personality traits in miners with past occupational elemental mercury exposure. Environ Health Perspect. 2006 ;114:290-6

Kokayi K, CH Altman , RW Callely, A Harrison. Findings of and treatment for high levels of mercury and lead toxicity in ground zero rescue and recovery workers and lower Manhattan residents. Explore (NY). 2006;2(5):400-7

McDonald EM, Mann AH, Thomas HC. Interferons as mediators of psychiatric morbidity. An investigation in a trial of recombinant alpha-interferon in hepatitis-B carriers. Lancet 1987;21;2:1175-8

Newman LS. Significance of the blood beryllium lymphocyte proliferation test. Environ Health Perspect. 1996;104(Suppl 5):953-6

Nuttal KL Interpreting mercury in blood and urine of individual patients. Ann Clin Lab Sci. 2004;34:235-250

Prochazkova J, Sterzl I, Kucerova H, Bartova J, Stejskal V. The beneficial effect of amalgam replacement on health in patients with autoimmunity. Neuro Endocrinol Lett. 2004;25:211-8

Roses AD. Apolippoprotein E and Alzheimer's diseass. The tip of the susceptibility iceberg. Ann NY Acad Sci, 1998;855:738-743

Seidenari S, Giusti F, Pepe P, Mantovani L. Contact sensitization in 1094 children undergoing patch testing over a 7-year period. Pediatr Dermatol 2005;22:1-5

Siblerud RL, Motl J, Kienholz E. Psychometric evidence that mercury from silver dental fillings may be an etiological factor in depression, excessive anger, and anxiety. Psychol Rep. 1994;74:67-80

Siblerud RL, Kienholz E, Motl J. Evidence that mercury from silver dental fillings may be an etiological factor in smoking. Toxicol Lett. 1993;68:307-10

Siblerud RL. A comparison of mental health of multiple sclerosis patients with silver/mercury dental fillings and those with fillings removed. Psychol Rep. 1992;70:1139-51

Stejskal V, Hudecek R, Stejskal J Sterzl I. Diagnosis and treatment of metal-induced side-effects. Neuroendo Lett 2006;27(Suppl 1):7-16

Stejskal V, Danersund A, Lindvall A, Hudecek R, Nordman V et al. Metal-specific lymphocytes: biomarkers of sensitivity in man Neuroendo Lett 1999;20:289-98

Stejskal V, Hudecek R, Stejskal J, Sterzl I. Diagnosis and treatment of metal-induced side-effects. Neuroendo Lett 2006;27(Suppl1):7-16

Stewart WF, Schwartz BS, SimonD, Kelsey K, Todd AC. APOE genotype past adult lead exposure and neurobehavioral function. Envorn Health Perspect 2002;110:501-505

Tirado V, García MA, Moreno J, Galeano LM, Lopera F et al. Neuropsychological disorders after occupational exposure to mercury vapors in El Bagre (Antioquia, Colombia)]. Rev Neurol. 2000;31:712-6

Turnbull A, Rivier C. Regulation of the HPA axis by cytokines. Brain Behav. Immunol 1995:253-275

Vozmediano JMF, Hita A. Allergic contact dermatitis in children. J European Academy Dermatol venerol 2005;19:42-46.

Valentine-Thon E, Schiwara HW. Validity of MELISA® for metal sensitivity. Neuroendo Lett. 2003; 24:57-64.

E Valentin-Thon, K Muller, G Guzzi, S Kreisel, P Ohnsorge et al. LTT-MELiSA® is clinically relevant for detecting and monitoring of metal sensitivity. Neuroendo Lett, 2006(Suppl 1); 27: 17-24

WHO Environmental Health Criteria, 1991;118:36

Wojcik DP, Godfrey ME, Christie D, Haley BE. Mercury toxicity presenting as chronic fatigue, memory impairment and depression: diagnosis, treatment,

susceptibility, and outcomes in a New Zealand general practice setting (1994-2006). Neuroendo Lett. 2006;27:415-23

Wright RO, Baccarelli A. Metals and neurotoxicity. J of Nutr. 2007;137:2809-2813

Zachi EC, Faria MA, Taub A. Neuropsychological dysfunction related to earlier occupational exposure to mercury vapor. Braz J Med Biol Res. 2007;40:425-33