

Does metal-induced hypersensitivity, a risk factor for venous stenosis and restenosis, contribute to brain and venous abnormalities in multiple sclerosis sufferers?

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OBJECTIVE Chronic cerebrospinal insufficiency (CCSVI) in patients suffering from multiple sclerosis (MS) is an important health affecting factor and can be treated by percutaneous transluminal angioplasty (PTA). However, Zamboni (1) reports that the real problem was restenosis after PTA, particularly affecting Internal Jugular Veins (IJVs), with over 50% of patients experiencing restenosis within 18 months. This study evaluates the evidence that metal induced hypersensitivity is a risk factor for both venous stenosis and subsequent restenosis after PTA.

METHODS and REVIEW OF EVIDENCE Hypersensitivity to transition metals such as nickel, cobalt or gold is an important risk factor of restenosis after cardiovascular stenting. Thus, cellular hypersensitivity (Type 4, delayed type allergy) to stent materials increases the risk for restenosis in patients with patch test positivity to nickel and cobalt (2) and recently in coronary patients with gold-plated coronary stents. (3,4) Thus, patients suffering from gold allergy proven by patch testing developed restenosis more frequently when compared to similarly treated non-allergic patients or patients with gold allergy but implanted with nickel or titanium-coated stents. Interestingly, the frequency of gold sensitization increases with the number of oral dental gold restorations. Further, in addition to cadmium and lead, which induce arrhythmias and high blood pressure, many studies indicate the role of mercury as a possible risk factor in cardiovascular diseases. (5,6) Titanium dioxide (TiO₂), a white pigment added into medication as well as to foods and cosmetics, activates vein endothelial cells *in vitro*, stimulates leucocytes and increases the production of inflammatory mediators, such as interleukins. It also increases the expression of ICAM1, E-selectin and VCA1 as demonstrated originally by Kirkpatrick and his group. (7) It has also been reported that titanium induces free radical formation and has prothrombogenic properties. (8) The iron deposition in the MS brain and the brains of patients with other neurologic diseases is a well-recognized phenomenon. In 1987, Dreyer and colleagues observed reduced signal density on T2 weighted magnetic resonance images (MRI) of the basal ganglia in the brain of MS patients and suggested that it is due to local iron deposition(9). Other studies confirmed this and revealed correlations between areas of low density in T2 weighted imaging and location of iron deposits as well as the correlation between the extent of gray matter T-2 hypointensity and MS progression(10) . Recently, Zivadinov and colleagues (11) reported that the degree of iron deposition correlated with venous obstruction in MS patients. This confirms previously published data of Zamboni's group (12,13) showing the clinical relevance of iron deposition in venous abnormality. Further, the authors suggest that iron deposition might correlate with disability and deterioration of MS patients.

RESULTS In an early study published by our group in Sweden in 1995, (14) iron deposits in basal ganglia were found in 34 patients with central nervous (CNS) and systemic symptoms but in none of the matched control group of 120 healthy volunteers examined by magnetic resonance imaging (MRI). The patients were referred by their doctors on the basis of suspected metal-induced inflammation/toxicity due to dental amalgams (so called silver fillings containing 50% of elemental mercury) or other dental metals. All patients suffered from CNS symptoms such as headache, dizziness, insomnia, nervous irritability, tinnitus, visual disturbances, memory impairment, inability to concentrate, mood swings and pronounced fatigue. Intensive investigation by neurologists, internists and specialists in infectious diseases could not find any diagnosis which could explain their CNS symptoms.

Twenty one of 34 patients suffered from atopic disease such as eczema and 12 patients were treated for hypothyroidism. Metal-specific hypersensitivity has been examined with an *in vitro* blood test, so called MELISA® test. (15,16) MELISA® is based on an idea that cultivation of blood lymphocytes containing memory cells together with a specific antigen, for example a metal salt, will result in stimulation and

proliferation of T cells. Overall MS patients showed a higher lymphocyte response to some metals as compared with healthy controls. The difference in metal reactivity was highly significant for inorganic mercury ($p < 0,001$), phenyl mercury and gold and weakly significant ($P=0,05$) for lead. These results were later confirmed in a larger group of over 100 patients suffering from MS compared to 144 healthy controls. In this study, MS patients exhibited significantly higher lymphocyte responses than healthy controls to the following metals: inorganic mercury, phenyl mercury, gold, palladium, cadmium, nickel and titanium.

The well-known accumulation of iron around the vein endings in the gray matter and the presence of lymphocyte and macrophages around demyelinating plaques could be due to dissemination of metal ions released from dying blood macrophages entering the brain through a damaged blood brain barrier. Local brain macrophages, oligodendrocytes, might further ingest the metal debris and become damaged in the process. Since oligodendrocytes are also cells producing myelin, the myelination process might be impaired as well.

CONCLUSION The data presented above indicate that transitional metals such as mercury, gold and titanium possess the capacity to trigger endothelial inflammation, T-cell metal-specific responses as well as free radical formation. Inflammation and free radical pathology is found in abnormal veins as well as in brain lesions of patients with MS. In summary, these findings point to the possible role of metal-induced sensitization in venous and brain pathology, found in patients with MS and other diseases. Therefore, the reduction of metal exposure, for example by replacing dental metals or by avoiding exposure to titanium dioxide coated (E171) medication and changing to titanium free medication, might improve the efficacy of PTA and decrease the recurrence of stenosis.

References: all available but cannot be included due to file size submission constraints. See www.melisa.org.

1. Zamboni P et al. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. *Journal of Vascular Surgery* Volume 50, Issue 6, Pages 1348-1358.e3, December 2009
2. Köster R, Vieluf D, Kiehn M, et al. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet* 2000; **356**: 1895-1897
3. Ekqvist S, Svedman C, Möller H, et al. High frequency of contact allergy to gold in patients with endovascular coronary stents. *Br J Dermatol* 2007;157:730-738.
4. Svedman C, Ekqvist S, Möller H, et al. A correlation found between contact allergy to stent material and restenosis of the coronary arteries. *Contact Dermatitis* 2009;60:158-164.
5. Virtanen JK et al. **Mercury, Fish Oils, and Risk of Acute Coronary Events and Cardiovascular Disease, Coronary Heart Disease, and All-Cause Mortality in Men in Eastern Finland**. *Arterioscler Thromb Vasc Biol.* 2005;25:228-233
6. Houston MS. Role of Mercury Toxicity in Hypertension, Cardiovascular Disease, and Stroke performed. *J Clin Hypertens (Greenwich)* 2011;13:621-627
7. Wagner M et al: Heavy metals ion induction of adhesion molecules and cytokines in human endothelial cells; *Pathobiology* 1997; 65: 241-252
8. Nemmar A, Melghit K, Badreldin H. The Acute Proinflammatory and Prothrombotic Effects of Pulmonary Exposure to Rutile TiO₂ Nanorods in Rats. *Exp Biol Med* 233:610-619, 2008
9. Dreyer BP et al. Magnetic resonance imaging in multiple sclerosis; decreased signal in thalamus and putamen, *Ann Neurol* 1987; 22: 546-550
10. Baksi R, et al. Gray matter T2 hypointensity is related to plaques and atrophy in the brain of multiple sclerosis patients. *J Neurol Sci* 2001; 185: 19-26
11. Zivadinov R et al. Use of MR venography for characterization of the extracranial venous system in patients with multiple sclerosis and healthy control subjects. *Radiology* 2011, 258: 562-570

12. Zamboni P et al. The big idea: iron-dependent inflammation in venous disease and proposed parallels in multiple sclerosis: 2010
13. Zamboni P et al. CCSVI in patients with multiple sclerosis J Neurol Neurosurg Psych 2009, 80: 392-399
14. Tibbling L, Thuomas KÅ, Lenkei R, Stejskal V. Immunological and brain MRI changes in patients with suspected metal intoxication. Int J of Occupational Medicine and Toxicol 1995; 4:285-294)
15. Stejskal V, Cederbrabt K, Lindvall A, Forsbeck M. MELISA-AN IN ViTRO TOOL FOR THE STUDY OF METAL ALLERGY *Toxic. in Vitro* Vol. 8, No. 5, pp. 99-1000, 1994
16. Stejskal V, Hudecek R, Stejskal J, Sterzl I. Diagnosis and treatment of metal-induced side-effects. *Neuroendocrinol Lett* 2006, 27 (Suppl. 1): 7-16