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Possible Relation Between Trace Element Status and Clinical Outcomes in Parkinson Syndrome

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1. Introduction

Parkinson disease (PD) is a degenerative disorder of the central nervous system and one of the most common neurologic disorders, affecting approximately 1% of individuals older than 60 years and causing progressive disability that can be slowed, but not halted, by treatment (Poewe, 2006; DeLong & Juncos, 2008). The epidemiology of Parkinson disease is not genetically predetermined, but influenced by environmental factors which may be geographically heterogeneous (Tanner & Langston, 1990). Major gene mutations cause only a small proportion of all cases and that in most cases; non-genetic factors play a part, probably in interaction with susceptibility genes (de Lau & Breteler, 2006). A number of environmental factors have been associated with an increased risk of Parkinson's including: pesticide exposure, head injuries, and living in the country or farming (Noyce et al. 2012; Van Maele-Fabry et al. 2012). Parkinson disease is characterised by focal loss of melanin –containing neurons of the central and caudal parts of the zona compacta of the substantia nigra (Jellinger 1987). Dopamine deficiency of the nigrostriatal system is the hallmark of PD disorder. The cause of the degeneration of the dopamine containing neurons in the substantia nigra of patients with PD is unknown. Excessive free radical production has been suggested as a consequence of the catabolism of the monoamines (Dexter et al 1989). It has been shown those catalase and glutathione peroxidases are reduced in the substantia nigra of PD patients (Sofic et al. 1992). It has therefore been suggested that additional antioxidant therapy including vitamins-E and C may be helpful to slowing the progression of PD. Increasing evidence indicates that PD is primarily a Mitochondrial disorder and thus the use of compounds With good mitochondrial penetrance, (CoQ10), could Potentially be of benefit in this disease (Matthews et al 1998).

2. Current treatment pathways

Parkinson's disease is a degenerative disease of the nervous system. The exact cause for Parkinson's disease is not well understood. There is no definitive test for PD – diagnosis is often based on medical history and the presence of the classic symptoms and signs of PD (Samii et al. 2004; Tolosa & Katzenschlager, 2007). Sometimes people are given anti-PD drugs to see if they respond, or other tests may be performed, such as MRI and CAT scans, to rule out other disorders with similar symptoms (Gelb et al. 1999; Hughes et al. 2002). The presence of other diseases, such as dementia and general ageing can obscure PD symptoms and reduce the chance of an accurate diagnosis. Certain drugs, when taken for long periods of time or in amounts greater than recommended, can cause Parkinsonism (Di Fabio et al. 2013) and have side effects. These medications do not result in Parkinson's disease, however, and symptoms resolve when the medications are no longer used.

3. Environmental and nutritional factors in Parkinson disease

Environmental factors and nutrients may play an important role in early life. In people who are genetically predisposed to Parkinson's disease, many experts believe that environmental exposures, such as unusual exposure to herbicides and pesticides, increase a person's risk of developing Parkinson's disease (Tanner & Langston, 1990; Van Maele-Fabry et al. 2012).

Numerous epidemiological studies and interventional trials have suggested a link, in aging, between an adequate nutritional status and health (de Lau & Breteler, 2006; Barichella et al. 2009). Nutrient deficiencies and constipation may also play a role (Dan Beth, 1992; Schelosky et al, 1995). Parkinson's patients are often deficient in vitamins, minerals and trace elements (Ames, 2011). Micronutrient sufficiency and quality of the lipid supply may play key roles in brain development. It is because of their diverse and vital roles that nutrient element imbalances are frequently found to be factors in degenerative diseases. Since the body cannot manufacture the elements-and daily losses are unavoidable-the nutrient elements are all "essential" and must regularly be taken in through the diet. Erythrocyte element levels are good indicators of body pools of essential elements such as selenium, zinc, magnesium, potassium, and calcium. Often referred to as minerals, the chemical elements are fundamental to every function in the body. It is because of their diverse and vital roles that nutrient element imbalances are frequently found to be factors in degenerative diseases. Since the body cannot manufacture the elements-and daily losses are unavoidable-the nutrient elements are all "essential" and must regularly be taken in through the diet. But they are easily lost in food processing, so it's easy to see how deficiencies can occur. It has been reported that moderate selenium and vitamin K deficiency show damage accumulates over time as a result of vitamin and mineral loss, leading to age-related diseases (Ames, 2006; McCann & Ames, 2011). Therefore, understanding how best to define and measure optimum nutrition will make the application of new technologies to allow each person to optimize their own nutrition a much more realistic possibility than it is today (McCann & Ames, 2011).

4. Oxidative stress and Parkinson's disease

Oxidative stress could play an important role in the degenerative process leading to Parkinson's disease. These considerations provide a rationale for therapeutic strategies to diminish oxidative stress in dopaminergic regions of brain. If oxidative stress is a major factor, the agents that selectively and safely chelate iron may be of value. It was reported that the mitochondrial deficiency (Shoffner et al. 1991; Jenner, 1991; Saggu et al. 1989; Perry & Yong, 1986) in electron transport, enhanced lipid peroxidation, elevated superoxide dismutase, diminished capacity to remove excess hydrogen peroxide (suggested by low glutathione and glutathione peroxidase levels) and the presence of increased iron, which catalyses formation of highly reactive hydroxyl ions from hydrogen peroxide, make attractive the suggestion that oxidative stress could play an important role in the degenerative process leading to Parkinson's disease (Ambani et al. 1975).

5. Selenium and other antioxidants in Parkinson

Deficiency of the minerals and other antioxidants required for life are relatively uncommon, however, modest deficiency is very common and often not taken seriously. Selenium is an essential trace element which is necessary for growth and protein synthesis. Selenium protects cellular elements from oxidative damage and may participate in redox type reactions. Low plasma selenium concentrations are associated with subtle neurological impairments reflected in soft neurological signs (Shahar et al. 2010). A statistically significant increase in plasma Se was identified for PD patients (McIntosh et al. 2012). This has been evidenced by an increased lipid peroxidation and reduced glutathione levels (Delanty and Dichter, 2000) and high concentration of iron and free radical generation via autocatalytic mechanisms within neuro-melanin-containing catecholaminergic neurons in the substantia nigra. In addition, the observation that exogenous administration of cysteine, N-acetyl cysteine or glutathione decreased the neurotoxic effects of 6-hydroxydopamine in vitro and in vivo reinforces this hypothesis (Soto-Otero et al. 2000). McCann et al. (2011), tested whether selenium-dependent proteins that are essential from an evolutionary perspective are more resistant to selenium deficiency than those that are less essential. The authors demonstrated a highly sophisticated array of mechanisms at cellular and tissue levels that, when selenium is limited, protect essential selenium-dependent proteins at the expense of those that are nonessential. It was also found that mutations in selenium-dependent proteins that are lost on modest selenium deficiency result in characteristics shared by age-related diseases including cancer, heart disease, and loss of immune or brain function (McCann et al., 2011). It was concluded that taking a multivitamin that contains selenium is a good way to prevent deficiencies that, over time, can cause harm in ways that we are just beginning to understand.

6. Zinc in Parkinson

Zinc is essential as a cofactor for a variety of enzymes and transcription factors and plays a role in various biological processes ranging from gene expression to the immune response. There are two distinct gene families of zinc transporters, 10 ZnT (Slc30a) and 14 Zip (Slc39a) transporter genes (Ohno et al., 1985; Liuzzi & Cousins, 2004). The zinc concentration is ~15 times greater in mature RBC than in plasma (Eide, 2006). More than 90% of RBC zinc functions as a component essential for the activity of zinc metalloenzymes, particularly carbonic anhydrase and Cu²⁺/Zn²⁺-superoxide dismutase (Ryu et al. 2008). Abnormal levels of Zn²⁺ plays a role in many diseases, including Alzheimer's and type-2 diabetes. Zn is an essential element for plants and other organisms and is involved in many cellular processes, including activation of enzymes, protein synthesis, and membrane stability (Welch et al., 1982). Zinc is involved in numerous aspects of cellular metabolism (Jiménez-Jiménez et al. 1992; Forsleff et al. 1998; Brewer et al. 2010). Zinc deficiency is characterized by growth retardation. The global extent of zinc deficiency is debated, but diets that are high in whole grains and low in meat could lead to deficiency (Qureshi et al. 2006; MacDiarmid et al. 2013). Low zinc supply has the same effect on human cells as on yeast, zinc deficiency might contribute to human diseases that are associated with a build-up of "junked" proteins, such as Parkinson's and Alzheimer's. A similar protective system to Tsa1 also exists in animals, and the research group plans to move ahead by studying that system in human cell culture (MacDiarmid et al. 2013). The authors demonstrated that cells that are low in zinc also produce proteins that counter the resulting stress, including one called Tsa1. Tsa1 could reduce the level of harmful oxidants in cells that are short of zinc (MacDiarmid et al. 2013).

It has been reported that zinc deficiency may be linked to increased inflammation. Liu et al (2013) studied the activity of zinc to control sepsis, the severe systemic response to infection that can lead to death. Using cell models, the team focused on the role of zinc to prevent the inflammation that leads to sepsis; they found that when a pathogen is recognized, the gene that produces the zinc transporter SLC39A8 (ZIP8) is expressed. This transporter then rapidly moves to cell's walls, where it shuttles zinc from the bloodstream into the cell; after cell entry, zinc is then directed to and bonds to a protein that halts further activity (Liu et al., 2013).

7. Is there a role for trace element in human diseases?

Trace elements are metal ions and non-metal ions (e.g. selenium, arsenic) in human body in low concentrations, less than about 0.05 %. Calcium in the body, about 1.4 % is usually considered a macro element but it should be kept in mind that inside cells calcium is present in low concentration as a trace element and needs carefully control as it is a powerful second messenger. Trace elements like vitamins must be added through food as the body can't synthesize trace elements. Some of them are essential e.g. lack may disturb metabolism, sometime causative a disease, Keshan disease. Some examples of essential trace elements: Si, Fe, F, Zn, Cu, Mn, Se, Mo, Co. Knowledge of trace elements has increased a lot since accurate,

sensitive, selective analytical technique was developed around 1980, ICP-MS (inductively coupled plasma mass spectrometry).

Trace elements were originally viewed as nutrients and they exert pharmacological actions. Some of these possibly essential elements also are receiving attention because of their toxicological or pharmacological properties that can affect health and wellbeing. However possible relation between trace element status and clinical outcomes are insufficient. Extraparamidal symptoms reflecting nigrostriatal dopaminergic hypofunction are common in patients with neuronal ceroid lipofuscinosis and Parkinson's disease. Inadequacy or imbalance of trace elements supply consequently affects a number of physiological functions. Zinc as an element that may play a protective anti-atherosclerotic role, decreases. Zn is considered an efficient antioxidant (Prasad, 2008). Zn controls metallothionein expression and is involved in, cellular redox regulation (Maret, 2000). Oxidative stress can be corrected by dietary Zn as demonstrated of hepatic antioxidant enzymes (Tupe et. al. 2010). Zn metabolism may be influenced by low intake, lack of protective factors, e.g. Se. Another possibility may be Cd competition with Zn. Cd has higher binding capacity than Zn, e.g. in metallothionein and may displace Zn from its carrier sites. In a study of Parkinson's disease Mn was implicated (Normandie and Hazell, 2002) and another study demonstrated elevated concentrations of Cd in the erythrocytes (Johansson et.al. 2007). Lack of protective elements e.g. selenium in the metabolism makes it easier for heavy metal ions to enter and interfere the metabolism. As trace elements are active in many parts of the cell metabolism the discussion will be focused on possible effects of imbalance due to heavy metal ions in Parkinson's disease.

8. Elemental profiles as an indicator of metal ion and ligand homeostasis

The cell metabolism is a complex balance of proteins, fatty acids, carbohydrates, metal ions and trace elements regulated by DNA and RNA in nucleus and mitochondria. As the metabolism involve many molecular reactions and species not practical to be monitored a simplified indication of metal ion-ligand status, elemental profile, may be a substitute to monitor effects of important cell reactions. The elemental profile may be looked upon as the integrated results of reactions at the moment the sample was taken. It is important to underline that deviations in the elemental profile may also include effects of compounds with strong association to the examined elements. These deviations may give biochemical and physiological insights to observe early changes in the metabolism. Changes of metabolism of metal ions in e.g. erythrocytes may help to understand early reactions, if it is normal or an indication of an early pathophysiological process.

9. Membrane trafficking and dynamics in presence of heavy metal ions

In a study of 12 patients (9 men and 3 women) with Parkinson's disease (Johansson et.al. 2013) erythrocytes showed significant increased concentration of Pb and Ag. The concentration

of Cd (9/12) was also higher than that of controls. The observed increased of concentrations of Pb, Ag and Cd may have effects at different levels, e.g. 1. ATP-metabolism and heavy metal ion metabolism 2. Pb, Ag, Cd interactions with dopamine metabolism 3. Axonal transport and membrane trafficking 4. ROS formation by increased activity of hemeoxidases and displaced iron 5. Preapoptosis signals and possible activation of second messengers 6. Pb and porphyrine synthesis

10. Possible sources of metal ion supply

10.1. ATP-metabolism and heavy metal ion interactions

Pb, Cd and Ag has higher association to binding sites than Mg, Ca. Possible effect is displacement of Mg from enolase enzyme which introduces a double bond in the phosphate group. Mg may also be blocked in the phospho-mutase reaction when phosphoglycerate is transferred from position 3 to position 2. Another effect of cadmium ions is inhibition of Na/K ATPase enzyme by 50% in ABC-transporters (Lijnen et. al. 1991). Examples above indicate possible effects of heavy metal ions in the ATP-metabolism.

10.2. Pb, Ag, Cd interactions with dopamine metabolism

In patients with Parkinson's disease the microenvironment is full of misfolded alfa-Synuclein (George et.al. 2013) in brain (striatum) which may promote aggregation of cells and cause losses in dopamine synthesis. The synthesis in substantia nigra may be blocked by the increased concentrations of Pb, Ag and Ag. Transport of compounds (dopamine, acetylcholine) by vesicles (Kornberg and McConnell, 1971) in axons may be blocked by reactions with heavy metal ions.

10.3. Axonal transport and membrane trafficking

The axonal transport of mitochondria (Hollenbeck and Saxton, 2006, Gunter et.al 2000) may be disturbed by Pb, Cd and Ag by carry over effects. Mitochondria were transported by kinosin, dynein and myosin motors (Zhang and Zhao, 2007). Interactions with the motor transport in axons may be expected to slow down or stop movements when exposed to Pb, Ag and Cd. The transport of Ca (Perin et.al.1990) may be blocked by Pb, Cd and due to stronger association to binding sites in the mitochondria and ER (endoplasmatic reticulum) resulting in poor nerve signals in the axons.

10.4. ROS formation by increased activity of hemeoxidases and displaced iron

The accumulated heavy metal ions in the erythrocytes may disturb oxygen transport and interact with important brain cells. Cd may be used in heme metabolism, reducing heme concentration when sufficient. In a previous study significantly increased concentration of Cd was observed in the erythrocytes (Johansson et.al. 2007). The gene for hemeoxygenases HO-1, HO-2 is Cd dependent (Koizumi et.al.2007, Alami et.al.2000). HO-1, HO-2 hemeoxygenases

are important for cleaning up residues of senescent erythrocytes. Low concentrations of Cd may be involved in cleaning up heme residues, too high concentration of Cd may support formation of reactive oxygen species (ROS), superoxide anion, hydroxy free radicals, and singlet oxygen. In the porphyrine synthesis it is important that introduction of iron (ferrochelatase, frataxin) is not blocked by excess Cd, Pb, Ag (Johansson et.al. 2007). Uncontrolled iron may react with oxygen and produce free radicals, Haber-Weiss reactions.

10.5. Preapoptosis signals and possible activation of second messengers

Cd may enter Ca channels (e.g. Gardos channels) in the erythrocyte membrane and introduce interactions in cells (Verboost et.al.1989). Cd, Pb, Ag may release Ca from calmodulin (superfamily of Ca-carriers) due to weaker binding. Ca is an important secondary messenger in cells activating e.g. flippases. Liberated Ca may activate translocators, flippases, within the cell (Devaux et.al. 2006). Phosphatidylserine in the inner leaflet may be transferred by translocators to outer membrane giving an apoptosis marker for the macrophages. Phosphatidylserine is normally situated below leaflet (Martin et.al. 1995). Increased Pb, Cd, Ag may start too early apoptosis of important cells e.g. neurons (Sopjani et.al.2009).

10.6. Pb and porphyrine synthesis

Pb is not known to be essential to man. Pb has redox capacity (Pb²⁺ or Pb⁴⁺) and usually associated in reduced form to other molecules. As about 99% of Pb is associated to erythrocytes in blood one target will be the metabolism of erythrocytes. Pb is known to interfere with aminolevulinic acid dehydratase in the heme synthesis (Flindt et.al. 1976, Kelada et.al.2001). Pb is also known to interact with Ca channels by allowing increased input of calcium starting too early senescence (Lang et.al. 2010).

10.7. Possible sources of metal ion supply

In the study of 12 Parkinson patients (Johansson et.al.2013) there was no information of food habits for individual patients. In Finland cadmium uptake from food is about 5-10 µg/day, lead 20-66 µg /day, silver was not mentioned. In Sweden cadmium uptake from wheat, rice, potatoes, root-crops is about 10-20 µg /day, lead 15-30 µg /day, silver was not reported. In view of contribution from nutrition of heavy metal ions it is interesting to note that cadmium rich diet in Nigeria decreased Hb and erythrocyte counts in mice (Asagba & Eriyamremu 2007). It cannot be excluded that cadmium, lead in food after long time may accumulate in human erythrocytes and likely decrease erythrocyte counts and hemoglobin synthesis. Smoker may have higher cadmium values in blood but there was no information about smoking habits. Implanters may be a source of metal ion supply. Amalgam is an alloy which is not stable but will release mercury, silver (Johansson E1991, Johansson E et.al.1994, Johansson E and Liljefors T, 1991). Studies indicate that released mercury from amalgam will be found in liver, kidney and brain only minor amounts of mercury will be found in the blood indicating need for looking after other indicators. The effects of silver are often missing but should be included due to effects of silver on important antioxidant compounds containing selenium, sulphur. Some amalgam fillings may have small sticks of guttapercha in the cavity. Some trademarks

of Gutta-percha contain cadmium but the released amount is not known for the examined patients (Johansson E and Liljefors T 1991). The observations of problems possibly attributed to implanters should be considered in the early diagnosis.

10.8. The discoid shape of erythrocytes and heavy metal ions

Erythrocytes must be able to shrink and expand during transport (Huang et.al. 2010). If Cd, Pb, Ag, are associated to stabilizing proteins, erythrocytes possess a spectrin-based cytoskeleton they may lose their capacity to shrink and expand (Zhang and Zhao, 2007, Bosman et.al. 2008) in the capillaries.

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