Chapter 3

Comparison of Erythrocytes for Individual Indications of Metabolism Changes in Parkinson's and Alzheimer's Diseases

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Abstract

Alzheimer's and Parkinson's diseases are neurodegenerative diseases where several biomarkers have suggested that a single measurement is not a sufficient biomarker. The observation of increased concentration of cadmium (Cd), lead (Pb), and silver (Ag) in erythrocytes by inductively coupled plasma mass spectrometry (ICP-MS) shows a need to look for new approaches to understand the complex synchronistic effects of the cell metabolism. We have used a simplified scheme to follow some of the effects by following a hierarchy of reactions simplified to monitor elements in peripheral blood cells, e.g., erythrocytes. Erythrocytes carry oxygen to cells and carbon dioxide and waste to the lungs and back when passing from different organs including the brain. Erythrocytes also have the capacity to carry metal ions, which may be transferred to other organs, e.g., brain, despite the blood-brain barrier (BBB) and choroid plexus filter. If transfer of Cd, Pb, and Ag is continued too long, the repair systems may not be sufficient, and epigenetic effects on DNA and RNA may begin. Peripheral blood cells, e.g., erythrocytes, may help get earlier individual indications of changes at the cell level by using ICP-MS.

Keywords: hierarchy, cells, Cd, Pb, Ag, erythrocytes, Alzheimer's disease, Parkinson's disease, epigenetic changes, element profile, ICP-MS

1. Introduction

The cell metabolism is a complex balance of proteins, fatty acids, carbohydrates, metal ions, and trace elements regulated by DNA and RNA in nucleus. The metabolism of proteins is

further influenced by a noncoding RNA, e.g., siRNA, which involves molecular reactions and metal ions. Reactions involving metal ions and molecules may create difficulties in interpreting which components are involved due to similar symptoms that may be created by different reactions at the cellular level, masking symptoms. A simplified summary of reactions is given in **Figure 1**.

In **Figure 1**, it is suggested that cell reactions proceed in a hierarchical manner, along with three main pathways [1]. The first pathway involves metal ions associated with ligands with different strengths due to properties of metal ions, binding compounds, pH, redox state, and medium where this reaction takes place. The second pathway involves organic compounds with nucleophilic or electrophilic properties resulting in products favoring the most reactive partner. The third pathway involves radical reactions which may be fast or slow depending on cell demand. The brain has high needs for oxygen and uses about 20% of the total oxygen. Oxygen is important for many reactions but can produce H_2O_2 or OH*– radicals that can cause severe damage when not under control. The reaction pathway used for processing a component will be dependent on DNA, RNA, and cell demand.

According to the Food and Drug Administration (FDA) [2], as many as 70% of drugs for Alzheimer's disease, 75% cancer diseases, 50% arthritis diseases, and 40% asthma diseases are

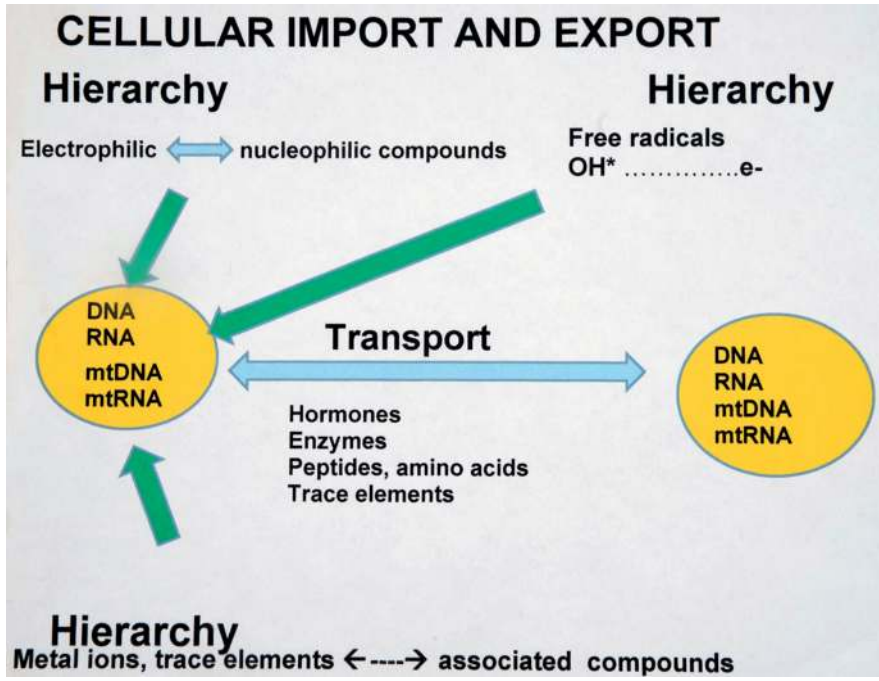

Figure 1. The flow of compounds and metal ions between cells is dependent on the three main chemical pathways in a hierarchy. The first path involves free radical-induced production of compounds where hydroxyl radical and solvated electron reactions may be involved. The second path involves electrophilic and nucleophilic compounds forming products adequate to the cells. The third path involves metal ions and ligands dependent on the previous two pathways but adapted to cell demand. The symbolic schedule indicates that compounds and metal ions may reach DNA and RNA not controlled by evolutionary developed genome adapted to cell demand. Small changes of DNA and RNA may take place, an epigenetic change, which may be restored or adapted, but large damages will present symptoms and are difficult to restore.

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not effective. The report may indicate compliance problems and difficulties with translating symptoms from reactions, but above all there is a need of more sensitive and selective systems to handle diseases.

Personalized medicine may be one way to improve systems by better diagnostic tools, designing drugs, etc. Peripheral blood has been used in medical diagnosis for a very long time, because, among other things, it is easily accessible. In the search for signs of lack or excess of minerals and trace elements in the disease, the interest has been focused mainly on blood, plasma, or serum. The utilization of blood cells as a marker model is proposed here. The element profile of blood cells may be one part to improve the present systems.

It is a challenge to separate normal reactions of cell metabolism from early pathophysiological differences. The identification of early changes in cells is important for correct diagnosis and optimal treatment when symptoms indicate the beginning of a disease. Blood cells which pass through several organs may be useful as they exchange information between systems involved. One example is the erythrocytes which transport oxygen from the lungs to different recipients and waste products back, e.g., CO_2 and hemoglobin, for decomposition and excretion. Besides the important transport of oxygen to oxygen-dependent organs, e.g., the brain, liver, and kidneys, they carry metal ions. When cells are growing old or have accumulated metal ions, the metabolism capacity of oxygen or transfer process of metal ions may be changed. By following the variations in the metal concentrations of the erythrocytes, summarized in an element profile, multifactorial diseases may be identified earlier. Observations of increased concentrations of metal ions, e.g., lead (Pb), (cadmium) Cd, and (silver) Ag, in the erythrocytes of patients with Alzheimer's and Parkinson's diseases by inductively coupled plasma mass spectrometry (ICP-MS) indicate possibilities to observe early steps in the pathophysiological processes and early epigenetic changes [3–5].

An early indication of changed metal ion homeostasis by an element profile is the change of important cell reactions. The element profile may be looked upon as the integrated results of reactions of metal ions and ligands. Cells with different life span, e.g., erythrocytes and platelets, help in the interpretation of possible changes. Changes in the element profile may give early biochemical, physiological, and pathophysiological information of changed cell metabolism and indicate defects in vulnerable organs.

2. Comparison of significant increased concentrations of Pb, Cd, and Ag in the erythrocytes of patients with Alzheimer's and Parkinson's diseases

Patients with Alzheimer's disease were selected in Finland [3] and patients with Parkinson's disease in Sweden [4, 5]. The mean concentrations of Pb in patients with Alzheimer' disease [3] and Parkinson's disease were 157 μg/kg (wet weight) and 67.8 μg/kg, respectively, about two times higher than that of Parkinson's disease [5]. The concentration of Cd in erythrocytes of patients with Alzheimer's disease was 11.5 μg/kg (wet weight) and 1.9 μg/kg in Parkinson's disease, about five times higher in Alzheimer's disease. An increased concentration of Ag was

observed in both Alzheimer's and Parkinson's diseases 7.4 μg/kg (wet weight) and 2.8 μg/kg, respectively, about two times higher in Alzheimer's disease. Pb, Cd, and Ag maintain the hierarchical effects on weaker associated metal ions in relation to association constants and not to DNA control when the balance of metal ions or binding compounds cannot be controlled [1]. It is important to identify early changes to understand the pathophysiological mechanisms and find proper treatments. Some effects will be discussed in relation to the imbalance of metal ion homeostasis and significant concentration changes of Pb, Cd, and Ag in the erythrocytes.

3. Reduced filter capacity of the kidneys and control of adrenal glands may promote the uptake of Pb, Cd, and Ag in erythrocytes

The reasons for the significant increased concentration of Pb, Cd, and Ag in erythrocytes of patients with Alzheimer's and Parkinson's diseases are not well understood. The absorption of essential elements starts in the small intestine, e.g., duodenum, less in the jejunum, and ileum, and large intestine. It is a complex interplay between intestinal bacteria and the liver, kidneys, pancreas, and bone. It is probable that Pb, Cd, and Ag may use the same carrier systems as essential elements in the blood. After the uptake of Pb, Cd, and Ag, they are transported to other organs for use or storage in the bone and also balanced by the kidneys and adrenal glands. The absorbed Pb, Cd, and Ag may not be properly controlled by the kidneys and adrenal glands. Excretion of Cd is very low and thus Cd is accumulated. The half-life of Cd in humans is about 20–35 years [6]. Most of the Cd is deposited in the kidneys, liver, pancreas, and lungs. Excess Pb is also accumulated often in the bone with a half-life of about 5–19 years [7]. The half-life of Ag in humans is not well documented, but an indicative value may be about 50 days [8]. Erythrocytes have a half-life of about 120 days. The accumulated silver in the erythrocytes may indicate a leakage of silver from root tips with silver amalgam [1, 9]. The contribution of Ag from food, drinking water, and vaccines is probably low. An imbalance of metal ion homeostasis in cell membrane carrier systems may interfere with essential element metabolism in favor of an epigenetic change. The decreased filter capacity of the kidneys and decreased control by parathyroid and adrenal glands can to some extent explain the accumulation of elements in the erythrocytes and the transport to other organs, e.g., brain. If imbalance of metal ion homeostasis in the erythrocytes is lasting too long, DNA control may decrease. The kidneys and adrenal glands in collaboration with the hypothalamus, pineal gland, pituitary glands, and choroid plexus are known to involve in the control of electrolyte and water balance [10, 11]. Chronic exposure to low concentrations of compounds with Pb, Cd, and Ag and loss of binding compounds, e.g., decreased available selenium and compounds with low metal binding capacity, may decrease the filter selectivity and disrupt DNA control. The background of decreased filter capacity is of course complex, but a part of the problem may be found in nutrition, e.g., lack of adequate selenium, phytate (inositol hexakisphosphate), flavonoids, and tannins balancing metal ion flux. In addition, environmental exposure, lack of exercise, smoking habit, and genetic factors may contribute. The decreased filter capacity of the kidneys and decreased brain control may promote the

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transport of metal ions and compounds not controlled by DNA, thus opening for epigenetic changes. Besides the transport of Pb, Cd, and Ag by erythrocytes in the blood, carriers like albumin, metallothionein, transferrin, and ceruloplasmin carry metal ions to recipients in the body. It is possible that the kidneys provide Pb, Cd, and Ag to erythrocytes, thus disturbing other carrier systems of elements, e.g., Na, K, Mg, Ca, and Se. It is not known if the imbalance of metal ion homeostasis in erythrocytes of patients with Alzheimer's and Parkinson's diseases starts in the kidneys and adrenal glands or how the imbalance of metal ions in the erythrocytes is transferred to other organs. The transport of Pb, Cd, and Ag from the membranes and further selection of metal ions are provided by different systems, e.g., transient receptor protein (TRP) channels [12–14], solute carrier (SLC) protein families [15, 16], and ATP binding cassette (ABC) families [17, 18] and calmodulin families [19, 20]. Interestingly, difference in binding capacity of the membranes gives an additional way to regulate metal ion flow controlled by DNA.

4. Increased concentration of Pb, Cd, and Ag in the erythrocytes and effects of messengers and cellular overload in metal ion homeostasis with reference to calcium homeostasis

The discussion will be limited to some effects of elements, which involve the important messengers in Alzheimer's and Parkinson's diseases: calcium, selenium, and inosine 1,4,5-triphosphate (IP3), the latter being an example of an organic messenger [21]. Calcium is an important intracellular messenger involved in the release of, e.g., [Ca^{2+}], from the rough and smooth endoplasmic reticulum (ER), ryanodine receptor, TRP, mitochondria, and calmodulin family, and apoptosis. Alterations in [Ca^{2+}] homeostasis have been suggested in neurological diseases, such as Parkinson's and Alzheimer's diseases [22–24]. The metabolism and flux of calcium in the ER are suggested to be dependent on, e.g., selenoprotein N, selenoprotein S, and selenoprotein T, critical for maintaining [Ca^{2+}] [25–27]. Microglia were implicated in Alzheimer's disease [28]. If Pb, Cd, and Ag enter in the microglia local defense systems, they may be decreased. Sodium and potassium ions are important for nerve signals and in glucose metabolism [29]. O'Brien and Legge [30] showed that erythrocytes may be mapped by using potassium ions with μ-PIXE technique resulting in a disclike structure indicating high concentration of potassium in the erythrocytes. Erythrocytes and neuron cells carry insulin receptors [31, 32]. Insulin facilitates the introduction of sodium-potassium pumps, indicating that insulin and insulin receptors also support the distribution of Na and K in membranes [33]. As Li, Na, and K often have lower affinity to receptors and carriers than Pb, Cd, and Ag, interactions can be expected in the uptake and transport of channels. In many cells, transport of K can be made in Ca channels, e.g., Gardos channels [34, 35], by SLC family [36]. Insulin facilitates the introduction of sodium-potassium pumps indicating that insulin and insulin receptors also support the distribution of these elements in neuron cells. Cd may interact with Na and K-ATPase, indicating a possible interaction with Na and K ions [37]. Ca and Mg in cells often are carried by members of calmodulin families [38]. Similar size of ionic radius of cadmium 0.97 A and Ca 0.99 A may explain competition of binding sites. Cd in calmodulin

molecule causes conformational changes of calmodulin [39]. The binding constants for Pb and Cd in calmodulin are higher than those of Mg and Ca. When cells are not controlled by DNA, Pb, Cd, and Ag may change the metabolism of Mg and Ca. It is not known if and how Pb, Cd, and Ag of erythrocytes compete with carrier systems of patients with Alzheimer's and Parkinson's diseases. In Alzheimer's disease acetylcholine receptors involve Ca [21, 40] which may be repressed by Pb, Cd, and Ag. In cells the calcium concentration is low and kept under strong control because correct concentration of Ca is important for the regulation of ATP synthesis in mitochondria and organelle functions. Uncontrolled release of Ca in cells disturbs ATP synthesis and apoptosis regulation. Cellular overload of Pb, Cd, and Ag is interesting in view of possible interactions of cell metabolism in three ways: (1) competition of Pb, Cd, and Ag with weaker associated metal ions as K, Mg, and Ca; (2) interaction of Pb, Cd, and Ag with selenium compounds in mitochondria and ER; and (3) reaction with phosphate groups in ATP and IP3. Reactive selenium compounds may be identified in different parts of ER important in the regulation of Ca [25]. Studies on harmful effects of metal ions often refer to one element at a time; very little is known about the effects of accumulated Pb, Cd, and Ag and their synchronistic damage. Dementia in Alzheimer's and Parkinson's diseases has been demonstrated in several studies [41]. The effects of Pb and Cd were demonstrated in mentally retarded children [42]. Pb, Cd, and Ag may also "hitchhike" endogenous carriers of essential metal ions making the interpretation of metal ion homeostasis not controlled by DNA reactions more complex. It is likely that Pb, Cd, and Ag may be able to repress Mg and Ca in cell DNA and disrupt DNA and RNA control due to synchronistic damaging effects.

5. Possible effects of Pb, Cd, and Ag on blood-brain barrier (BBB) filter and choroid plexus in relation to metal ion imbalance and selenium homeostasis

In Alzheimer's and Parkinson's diseases, malfunctions may be attributed to damage in different regions. The transport of compounds and metal ions to the brain is controlled by blood-brain barrier and by CSF in the choroid plexus [43–45]. The blood-brain barrier is constructed of endothelial cells, astrocyte end-feet, and pericytes forming diffuse barriers, tight junctions, receptors, and channels for carrier-mediated transport [46]. Leukocytes and larger molecules cannot pass into the BBB as well as in other vessels, but, e.g., oxygen, carbon dioxide, iron, glucose, and certain amino acids can pass. If Pb, Cd, and Ag from erythrocytes enter the BBB, an imbalance may be expected of metal ions and compounds in regions of, e.g., the hippocampus, hypothalamus, pituitary gland, pineal gland, and cortex. Part of Pb, Cd, and Ag in the erythrocytes may "hitchhike" tight junctions, channels, and carriers for essential elements in BBB and enter neuron cells, astrocytes, and microglia in a way not controlled by DNA. Pericytes and endothelial cells have mitochondria and ER which need selenium for proper function of, e.g., Ca and Mg. Mitochondria synthesize ATP, and lowered selenium and Mg may decrease the production of ATP and complicate synthesis systems in ER for the control of Ca and Mg. Activated neutrophil granulocytes can produce (H_2O_2) damage in tight junctions and receptors in membranes of pericytes and endothelial cells when there are local

low selenium status and low activity of protecting GSH-Px (GPx1 and GPx4). The ER stores selenium [25] and metal ions for maintaining calcium metabolism. Imbalance in metal ion homeostasis and selenium homeostasis can hamper DNA control of metal flux to different organelles, e.g., ER, mitochondria, Golgi, and nuclei. Besides erythrocyte transport of Pb, Cd, and Ag, albumin may carry Pb, Cd, and Ag which can react with tight junctions and receptors on pericytes and pass, loaded with Pb, Cd, and Ag producing reactive oxygen species (ROS). Pb, Cd, and Ag can interact with elements in mitochondria, e.g., Mg, Ca, Mn, and Se, and disturb ER storage of calcium and action of selenophosphate synthetase. The introduction of selenium in amino acids and UGA (stop codon) is very important for cell metabolism. Albumin may carry heme groups having an antioxidant effect, which decreases the risk of ROS production [47]. Microglia can attack receptors and tight junctions on pericytes around the endothelial cells producing ROS damage and perhaps open for albumin entrance carrying Pb, Cd, and Ag. The brain is composed of 80% water and uses aquaporin, AQ1, AQ4, and AQ9, for water balance [10]. Apart from water control, Pb, Cd, and Ag can use aquaporin for passage [11]. If Pb and Cd can pass into the mitochondria, Mn may be displaced and trigger SOD to produce ROS. Pb, Ca, and Ag may use the SLC system [48], "hitchhike," and transfer elements through the BBB in a way not controlled by DNA. Choroid plexus epithelial cells are rich in selenium [25] and may act as an additional barrier against metal ions and toxic compounds [43]. If erythrocytes are overloaded with Cd, Pb, and Ag, some ions may pass the BBB in other regions of the brain, e.g., hippocampus and cortex, and produce local imbalance of metal ions and selenium homeostasis in the brain.

6. Effects of Pb, Cd, and Ag on insulin receptors in brain cells and energy homeostasis

Increased concentrations of Pb, Cd, and Ag do not only affect the transfer of metal ions but also may influence the metabolism of proteins and peptides [49–51]. In plasma about 30% of Ca and about 40% Zn may be carried by albumin, but albumin also carries other elements and organic compounds [47, 52–54]. In the study of albumin, Pb and Cd decreased the transport of taxifolin [55]. Albumin in the blood carries 1–10% of glucose. If Pb, Cd, and Ag bind to albumin, transport of organic compounds, e.g., glucose, may be decreased. Many peptides and proteins in the BBB are transported by carrier in membranes, e.g., SLC and ABC families, which can be blocked by Pb, Cd, and Ag. T4 (thyroxin) in the blood is transported by transthyretin to the BBB [56]. T4 is dependent on selenium deiodinases for transfer to active T3 (thyronine) [57]. As both deiodinases and T4 and T3 have reactive selenium and iodine groups can Pb, Cd, and Ag disturb selenium homeostasis. Insulin present in the brain is not known to be directly involved in glucose metabolism but may assist in the regulation of energy homeostasis [49, 50]. The brain has many insulin receptors, which is highest in the hippocampus. The association of metal ions to insulin receptors in neuron cells may be similar as that of erythrocytes when Cd, Pb, and Ag interact with K^+ and Na^+ ions with insulin receptors [32]. Insulin binding sites to insulin receptor may be occupied by Pb, Cd, and Ag and decrease transport. Memory problems connected to the hippocampus may be explained to some extent by a decreased

transport of insulin, availability of glucose, and the antioxidant capacity of the brain involved in energy homeostasis [49, 50]. If the concentration of Pb, Cd, and Ag of the erythrocytes is too high, insulin transport in the brain may be decreased with less capacity to control energy homeostasis and hormone balance of insulin, leptin, and serotonin [49].

7. Axonal transport and possible interactions of Pb, Cd, and Ag

The axonal transport of mitochondria [58, 59] may be blocked by Pb, Cd, and Ag. Mitochondria were transported by kinesin, dynein, and myosin motors. Accumulation of Pb, Cd, and Ag in the erythrocytes may interact with transport in neurons due to carry-over effects.

In the synapse dopamine and acetylcholine are transported in the vesicles. The observed accumulation of Pb, Cd, and Ag in the erythrocytes may present two problems: (1) lowered dopamine production and (2) blocking acetylcholine.

Dopamine synthesis may be disturbed by Cd, Pb, and Ag in the medulla of adrenal glands, neuron cells, and substantia nigra. Transport of molecules, e.g., dopamine, may be blocked by Pb, Cd, and Ag. Interactions with aldosterone formed in cortex (adrenal glands) are known as an important regulator of Na, K may be disturbed. The high concentration of Cd, Pb, and Ag may interact with the hormone controlled by, e.g., hypothalamus, thalamus, and adrenal glands.

8. Changed metal ion and selenium homeostasis by overloaded Pb, Cd, and Ag in erythrocytes related to receptor functions in Alzheimer's and Parkinson's diseases

Important calcium-dependent receptors were reported in Section 3. Receptors may respond to metal ions and compounds but in a hierarchy to respond correctly. Receptors in the different brain regions may need to be restored; excess Pb, Cd, and Ag may block restoring procedures. Receptor feasibility is dependent on metal ions and organic compounds to maintain hierarchy in selectivity and efficacy. If receptors are exposed to overload of Pb, Cd, and Ag in erythrocytes, receptor activity may be destroyed or renewal not be possible. Patients with Alzheimer's and Parkinson's diseases with changed metal ion homeostasis meet incomplete selenium proteins or not properly adapted proteins [60, 61]. In Parkinson's disease, dopamine synthesis in neuron cells, e.g., substantia nigra and hypothalamus, is decreased. In parkinsonian patient's postmortem substantia nigra, increased concentration of iron was observed [62]. Transport of iron by SLC41 (membrane iron carrier) to the substantia nigra can be disrupted by erythrocytes overloaded with Pb, Cd, and Ag and decrease the synthesis of dopamine. Lowered Ca homeostasis is coupled with selenium deficiency in ER in both Parkinson's and Alzheimer's diseases [26, 63–69]. In Alzheimer's disease increased production of β-amyloid is implicated. Patients with Alzheimer's and Parkinson's diseases may have in common increased Pb, Cd, and Ag in the erythrocytes with possible interactions with

selenoproteins and phosphate groups in nuclei, ER, mitochondrial ATP, and IP3 [27]. SelP (selenoprotein P) in the brain with about 10 Se atoms is important to support different brain regions with selenium. As SelP is very reactive, Pb, Cd, and Ag and their protective role may be blocked [70]. A more basic work is necessary to understand how the regulation of metal ion homeostasis in cells is related to selenium homeostasis at the local level.

9. Epigenetic effects on DNA and RNA repair systems after exposure to Cd, Pb, and Ag from erythrocytes

Cells exposed to Cd, Pb, and Ag can disturb the genomic stability which is dependent on Mg [71, 72]. DNA is dependent on efficient repair systems due to as many as 10,000 errors/cell/day [73]. If Cd, Pb, and Ag from erythrocytes are introduced to cells, repair systems will not work properly [74]. Deformed molecules or decreased production of important protective compounds may initiate problems in cell metabolism, e.g., it starts wrong apoptosis signals and Cd, Pb, and Ag may compete with repair systems, e.g., enzymes and ligases of DNA polymerases [75, 76]. Excess Cd, Pb, and Ag can also impair Zn-dependent RNA polymerases by competing with the active center in the binding domain and also create cross-linking of DNA [77–79].

10. Conclusions

ICP-MS may be used for the determination of the element profile of erythrocytes as a biomarker in Alzheimer's and Parkinson's diseases. The increased concentration of Pb, Cd, and Ag in erythrocytes in Alzheimer's and Parkinson's diseases indicates changes in the filter capacity of the kidneys combined with the changes of the adrenal glands. Studying multifactorial problems using element profiles in diseases may help to identify early changes in the pathophysiological process and epigenetic progress. The increase of Pb, Cd, and Ag in the erythrocytes may indicate changes in metal ion homeostasis at the cellular level in other parts of the body, e.g., the brain.

Parkinson's and Alzheimer's diseases are neurodegenerative diseases. A variety of treatment recommendations in the treatment guidelines have been proposed, including physical activity and disease-modifying medication, which should be initiated at the early stage of the disease. The complex synchronistic effects at the cellular level when Cd, Pb, and Ag enter in a noncontrolled way may be approached by using ICP-MS. It is hoped that this knowledge will allow the identification of novel therapeutic targets that will eventually lead to a more efficient treatment, based on the patient's individual genetic predispositions.

Many candidate biomarkers of the neurodegenerative diseases have been proposed in the scientific literature, but in all cases, their variability in cross-sectional studies is considerable, and therefore no single measurement has proven to serve a useful marker, possibly lacking the power of directly predicting disease risk, as the underlying physiological change may per se be harmless and without functional compromise.

This necessitates the development of new effective strategies for the prevention and early diagnosis of such conditions. Contrary to the common perception that personalized medicine is completely based on a genetic approach, clinical subtypes, personality, lifestyle, aging, and comorbidities constitute the true personalized medicine.

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