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High incidence of Parkinson disease in patients with chronic hypoxia

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Abstract: The cost of Parkinson's disease is substantial, including reduced quality of life, lost productivity, and increased health care expenditures. The lung diseases are the trigger cause of Parkinson and other neurodegenerative diseases; many cohort studies approved the relation worldwide, but southern cities have special identity of sandy weather at most of our time, rather than a type of work in cement factories. The increasing number of lung disease incidence was elevated at last 10 years ago rapidly, which increase the probability of relation, therefore, we stepped the time engine to approve the highly incidence of Parkinson disease and chronic ischemia. The experiment had conducted 10 patients with PD and measured the parameters in relation to hypoxia like hemoglobin content, iron, and uric acid, and compared the results with normal control using unpaired t-test. P-value ≤0.005 was considered to be statistically significant. The hemoglobin content in blood of Parkinson disease patients are expressed a significant inhibition with P≤ 0.05, compared to normal control (13 g/dl). While, the blood ferratin content of iron is considered the bridge line which connect the lung with the other parts of body. Hypoxia inducible factor -1 has ability to regulate a series of genes that control the iron homeostasis. The results of research have indicated significant sinking in iron level compared to normal control (100 ng/ml). It's clear declining in level of uric acid in Parkinson's patients comparing with normal control (6.3 mg/dl). It has been approved that lung disease increases the risk of Parkinson disorder via many metabolic and genetic pathways mainly the hypoxia; the situation that support using of iron tablet as drug of suggestion in mild cases rather than levodopa with its suppression side effect.

Keywords: Parkinson, Hypoxia, iron

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder and with the accelerated ageing of human society, expectedly, its distribution is increased by future[1]. It was originally described by James Parkinson and is named for him. Parkinson disease (*paralysis agitans*)is degeneration of the dopaminergic neurons of the pars compacta of the substantia nigra, which leads to deficiency of dopamine in the striatum.

Akinesia show involuntary tremor with solidity in movement. However, the dopamine secreted in the caudate nucleus and putamen is an inhibitory transmitter; therefore, destruction of the dopaminergic neurons in the substantia nigra; theoretically would allow the caudate nucleus and putamen to become overly active and possibly cause continuous output of excitatory signals to the corticospinal motor control system. These signals could overly excite many or all of the muscles of the body, thus leading to rigidity[2,3].

Lead pipe rigidity is a behavior dead-feeling resistance; sometimes a series of "catches" takes place during passive motion called cogwheel rigidity. The tremor, which is present at rest and disappears with activity, is due to regular, alternating 8-Hz contractions of antagonistic muscles. In Parkinson disease, the dopaminergic input to the putamen is lost. This results in decreased inhibition and increased excitation from the Sub thalamic nucleus (STN) to the interior part of Globus Pallidus (GPi). The overall increase in inhibitory output to the thalamus and brain stem disorganizes movement[4].

The brain is extremely sensitive to hypoxia, and basal ganglia use O2 at a very high rate, and symptoms of Parkinson disease can be produced by chronic hypoxia. The thalamus and the inferior colliculus are also very susceptible to hypoxic damage. The symptoms produced by chronic exposure to sublethal concentrations of CO are those of progressive brain damage, including mental changes and, sometimes, a parkinsonism-like state[5]. Accidently discovering of heroin containing MPTP could enhance the induction of disease via the inhalation, it's by the metabolism of 1-methyl-4-phenylpyridinium (MPP+)[6]. It was found that patients with PD had lower serum levels of uric acid than healthy controls[7].

Hypoxia inducible factor-1 (HIF-1), a heterodimer consisting of expressed b subunit and an oxygen-regulated a subunit, is a transcriptional factor responsible for cellular and tissue adaption to low oxygen. Pharmacological inhibitors of the iron-dependent enzyme class prolyl hydroxylases (PHD), which target alpha subunits of HIF proteins for degradation, have recently been demonstrated to elevate neurodegeneration associated with stroke and hypoxic-ischemic injuries.

Recent studies have shown that HIF-1 can increase dopamine synthesis and dopaminergic neuron growth. Moreover, HIF-1 may protect dopaminergic neurons through the alteration of iron homeostasis and defense against oxidative stress and mitochondrial dysfunction, which suggests that HIF-1 may potentially have medical value for treating neurodegenerative diseases[8].

The lung diseases are trigger cause of Parkinson and other neurodegenerative diseases; many cohort studies approved the relation worldwide, but southern cities have special identity of sandy weather at most of time, rather than a type of work in cement factories. The increasing number of lung disease incidence was elevated at last 10 years ago rapidly, which increases the probability of relation, therefore, we stepped the time engine to approve the highly incidence of Parkinson disease and chronic ischemia.

MATERIALS AND METHODS

Blood collecting and sampling: A total of 10 blood samples were collected during the period from September 2016 to April 2017 in the Neurology and Psychiatry department of Al-Naseriah hospital. Records of ages and sex obtained from the statistics unit of the hospital for 10 patients of Parkinson and 10 non Parkinson as control. Blood was collected with the 5cc syringe, collecting the blood in containers with EDTA-K_3 to a total volume of 2.5 ml, keeping the residual part without coagulant for biochemical tests[9].

Hemoglobin determination methods (HB %): Methods for hemoglobin determination are many and varied. The most widely used automated method is the cyanmethemoglobin method**.** To perform this method, blood is mixed with Drabkin's solution, a solution that contains ferricyanide and cyanide. The ferricyanide oxidizes the iron in the hemoglobin, thereby changing hemoglobin to methemoglobin. Methemoglobin then unites with the cyanide to form cyanmethemoglobin. Cyanmethemoglobin produces a color which is measured in a colorimeter, spectrophotometer, or automated instrument. The color relates to the concentration of hemoglobin in the blood. Place 5 ml of Drabkin`s solution in test tube. Gets 0.02 ml of whole blood using Sahli pipette. Rinse the blood into Drabkin`s solution. Mix and let it stand for 10 min. Then read in a spectrophotometer at 540nm. Prepare a graph of the standard solutions and determine the concentration of each unknown. The normal values for hemoglobin determinations are 12.5- 15 g/dl in woman, while 14-17g/dl in man[10].

Blood iron value: Blood iron value was measured by colorimetric method, with commercially available kit (bio merriex, Frence). Principally, addition of acid HCl to sera release iron from transferrin (by lowering the pH and precipitation of sera proteins (FeIII), in the supernatant is reduced to (FeII) and determined quantitavily by photometric measurement at the absorbance of the colored complex formed between FeII and Ferrozine as chromogen (Ferrozine composed of 3-(2-pyridal)-5,6-bis(4-phynel sulfonic acid)-1,2,4-triazine, monosodium , monohydrate)[11]. The complex read spectrophotometrically. Non-coagulant blood should be used because EDTA chelating is changing the results mistakenly;moreover, avoiding hemolysis because of the affinity of iron to released hemoglobin molecules.

Uric acid: Sera uric acid was measured by enzymatic method, with commercially available kit (bio merriex, France). The reaction of uric acid with peroxide by activation of uricase produce a photometric chromagen could be measured in 520nm by UV-visible spectrophotometer[12].

Statistical analysis: Standard statistical methods were used to determine the mean and standard deviation (SD).Unpaired t-test was used to compare the results of different biochemical parameters of patients with PD with the controls. P-value ≤ 0.005 was considered to be statistically significant[13].

The Results

It's approved that anemic status is an essential factor for Parkinson disease, which is a reason to suggest a test.The hemoglobin content in blood of Parkinson disease patients are expressed a significant inhibition with $P \leq 0.05$, compared to normal control as it is shown in a Figure 1. The Hb content did not decrease to known level of anemia, rather than the overall appearance of patients. Its normal values within low limits in elders populations (13 g/dl).

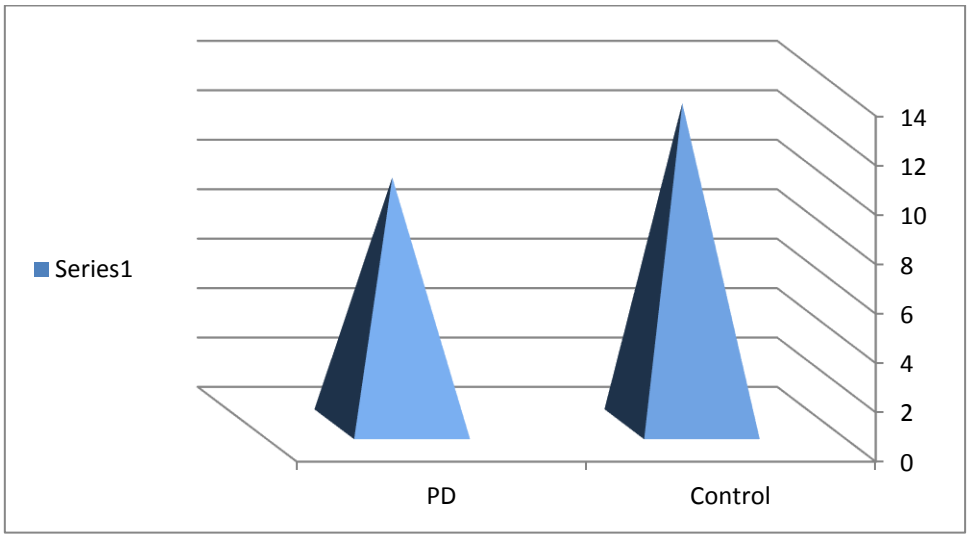

Figure 1: Illustrate the Hb content in blood of Parkinson patients in contrast to normal control. The results have significant differences P≤0.05.

While, the blood ferratin content of iron is considered the bridge line which connect the lung with the other parts of body; Hypoxia inducible factor -1 has ability to regulate a series of genes that control the iron homeostasis. The results of research indicated a significant sinking in iron level, P≤0.05 as it's shown in a **Figure 2**. The iron level did not drop to state of anemia, but it's still below the normal range.

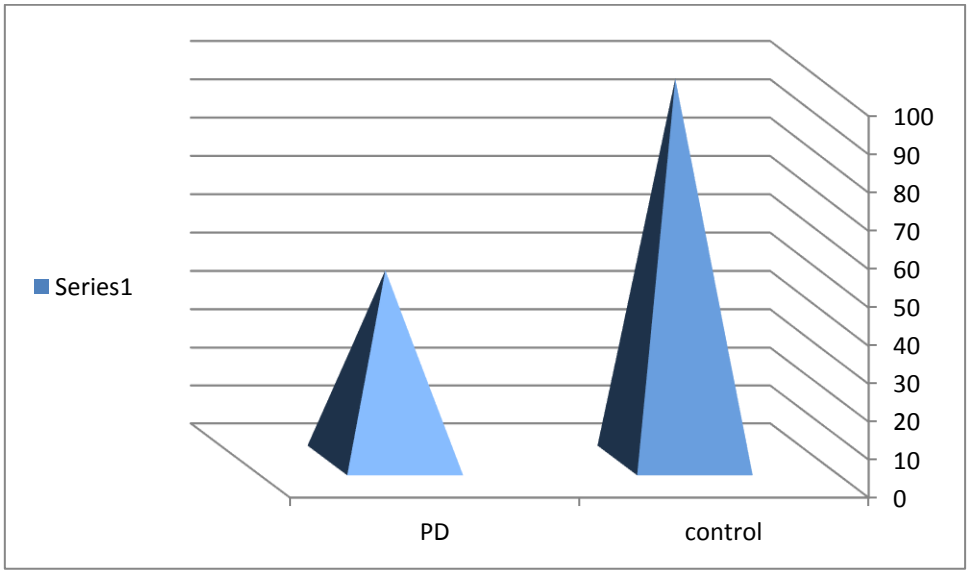

Figure 2: Illustrate the iron content in blood of Parkinson patients in contrast to normal control. The results have significant differences P≤0.05.

Uric acid is antioxidant biomarker; it's free radicals scavenger, the reason why it's been chosen in the research. Its level increased with inflammation, smoking, dusty weather, radiations, and metabolic disorders. In this research its clear declining in level of uric acid in Parkinson's patients comparing with normal control P≤0.05, as it's shown in **Figure 3**.

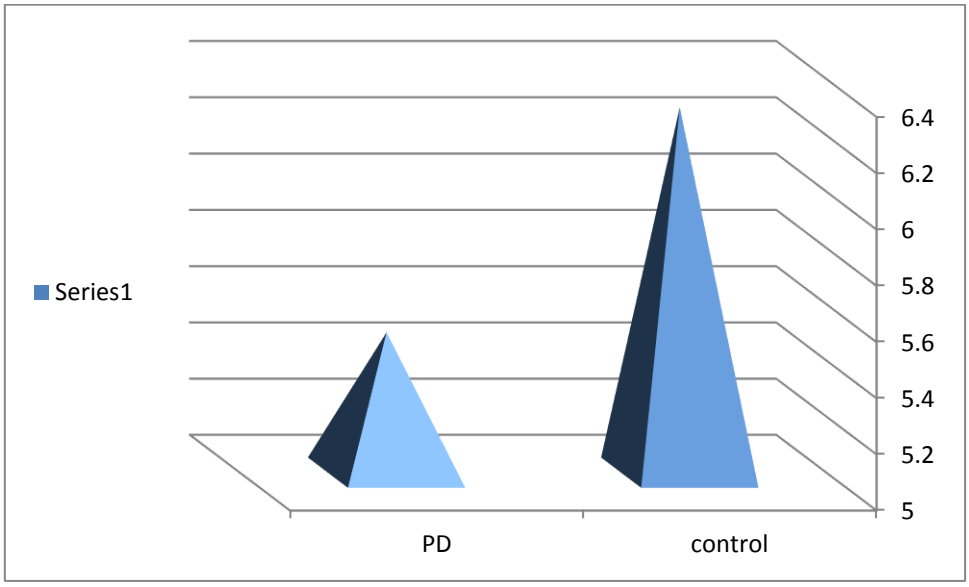

Figure 3: Illustrate the Uric Acid level in blood of Parkinson patients in contrast to normal control. The results have significant differences P≤0.05.

DISCUSSION

Diagnosis of Parkinson disease is based on clinical impression of symptoms and neurological examinations, and recently evidences from bio-imaging techniques seem to be valuable in late stage of disease. Bradykinesia, resting tremor, rigidity, and impaired gait are the main symptoms of disease; further, anxiety and stress intolerance are commons[14]. There is no specific laboratory method to confirm the diagnosis because the disease is a result to many genetic and environmental factors regretted the dopamine production. Although data from cohort studies suggest that hypoxia is a risk factor for PD, there is no strong evidence on this LinkedIn. Further prospective studies focused on putative pathogenic pathways and taking a broad range of confounders into account is required to clarify this relationship[15].

The present study has revealed that hemoglobin content in blood of Parkinson disease patients are expressed a significant inhibition with P≤ 0.05, compared to normal control. Inhibition level did not cross the threshold of anemia but still under the normal condition. Hypoxia has many aspects of effect rather than prevent the oxygen passage to lung as usually understood; it's broadband to comprise the pathways of oxygen transition within the body. Therefore, estimation of Hb is a method of choice to detect the internal hypoxia in Parkinsonism. The results indicated a clear correlation between the Parkinson patients and their Hb content; it's supportive evidence to this relation (13 g/dl). It's not off coarse each case of anemia led to PD, but it's certainly all cases of PD suffer Hb decrease.

Previous studies have demonstrated that deferoxamine, an iron chelator, can activate HIF-1_ and prevent neuronal death in both *in vitro* and *in vivo* models of ischemia likely via inhibition of Prolyl hydroxylase PHDs [16]. The results of research indicated a significant sinking in iron level, P≤0.05 compared to control. It has been demonstrated that iron chelation was effective in significantly

attenuating1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine MPTP-induced DAergic nigral neurode-generation via overexpression of the iron-storage protein ferritin in DAergic neurons and pharmacological chelation of iron by the blood-brain barrier-miscible metal chelator clioquinol. Specific potential mechanism(s) involved in the protective effects of iron, however, were not explored. Prolyl hydroxylases are iron-dependent enzymes that reduce levels of HIFs via their ability to hydroxylate these proteins[17]. The study approved the relation between declining of iron level in cases of hypoxia and Parkinson disease, the situation that support using of iron tablet as drug of suggestion in mild cases[18]. HIF-1 regulates a series of genes that participate in angiogenesis, iron metabolism, glucose metabolism and cell proliferation and survival[19]. Under hypoxic or iron lacking conditions, PHDs are prevented from hydroxylating proline residues within the alpha subunits of the HIF protein, preventing the degradation of the protein[20].

The ground state of oxygen is essential for respiration. However, the oxygen imbalance derives into toxicity. Oxidative stress is imbalance between the reactive oxygen species (ROS) from reactive oxygen, reactive nitrogen species (RNS) from reactive chlorine and antioxidants. Free radicals harm the biological systems and cause the inflammation. The brain is particularly vulnerable to oxidative stress as it is considered an 'expensive tissue' with a particularly high metabolic rate and comparatively increased utilization of oxygen. Brain tissue is also high in unsaturated lipids, which makes it more susceptible to free radical damage. With regard to antioxidant status, this study reported that uric acid levels were lower in patients with PD. Its importance came from the scavenging work of free radicals. Many researchers reported a significant decrease in uric acid of patients with Parkinson[21-23]. Which supported this research etiology and relation of hypoxia with parkinsionism.

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