Original Article

Defective Systemic Iron Metabolism in Parkinson's Disease

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Background : Biochemical, histopathologiacal and in vivo brain imaging techniques, such as magnetic resonance imaging and transcranial sonography revealed a consistent increase in substantia nigra iron in Parkinson's Disease. Under normal condition iron status influences the synthesis of major proteins of systemic iron metabolism (eg, Ferritin, Transferrin, Transferrin receptor). Iron deposition in substantia nigra in Parkinson's Disease has been associated with systemic defect in the regulation of iron metabolism and storage. Remarkably, there is few data available concerning to overall systemic iron metabolism in Parkinson's Disease. So, we measured blood hemoglobin levels, Serum Iron and Total Iron Binding Capacity (TIBC) in patients with Parkinson's Disease and controls.

Materials and Methods : A total 104 subjects, including controls, were enrolled in the study and further grouped as, 52 clinically examined Idiopathic Parkinson's Disease patients (35 males and 17 females) while remaining 52 were taken as age and sex matched healthy controls. Two tailed student 't' test was used for statistical analysis.

Results: We found concentration of blood hemoglobin ($p>0.05$) not differ statistically in Parkinson's Disease patients and controls. Further we observed Serum Iron ($p<0.001$) was significantly lower in Parkinson's Disease patients as compared with controls and TIBC not increased as expected in systemic iron metabolism, but it was significantly decreased ($p<0.05$) in Parkinson's Disease patients as compared with controls.

[*J Indian Med Assoc* 2024; **122(6):** 52-4]

Key words **: Serum Iron, TIBC, Parkinson's Disease.**

Parkinson's Disease (PD) is a disorder of the central nervous system, involving primarily a degeneration of certain nerve cells in deep part of brain called basal ganglia, and in particular a loss of nerve cells (or neuron) in a part of brain stem called Substantia Nigra (SN). These cells make a neurochemical messenger dopamine, which is partly responsible for starting a circuit of messages that coordinate normal movement. In absence (or with substantial reduction, more than 80% of normal level) of dopamine, the neurons in the receiving area (called dopamine receptors) in the next part of the basal ganglia circuit called the striatum are not adequately stimulated and the result is impairment of movement with tremor, slowness, stiffness, or balance[1].

For many years it was believed that iron enter in the brain mainly during infancy before the blood brain barrier get matured. However, in the last decade, it has become apparent that brain-iron uptake is mediated by endothelial Transferrin Receptors (TFRs) expression in blood brain barrier of adult animals and this TFRs expression on the luminal endothelial surface is regulated by the iron status of central nervous system[2,3].

Editor's Comment :

- Existence of a defect in the system that regulates the synthesis of major proteins of iron metabolism occurred, not only in the brain but also in the liver of Parkinson's disease patients.

Evidences suggest that the pathogenesis of PD may relate to abnormality in the regulation of the major proteins of iron metabolism[4]. Very little information exists concerning overall systemic iron metabolism in PD. Using a case control design, we tested the hypothesis that overall systemic iron metabolism disrupted in PD, as it was already observed in the brains of PD patients[5]. For that, we measured concentration of blood hemoglobin levels, Serum Iron and TIBC in PD patients and compared with controls. Concentration of hemoglobin levels not differ statistically in PD patients and controls. We now report that PD is associated with significant reduction in Serum Iron as compared with controls. Further significant reduction of TIBC in PD patients as compared with control was unexpected.

Materials and Method

The present study was conducted in Department of Biochemistry, Bidar Institute of Medical Sciences, Bidar. A total 104 subjects, including controls, were enrolled in the study and further grouped as, 52 clinically

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Received on : 18/02/2023

Accepted on : 23/02/2023

examined Idiopathic Parkinson's disease patients (35 males and 17 females) while remaining 52 were taken as age and sex matched healthy controls. The study was approved by institutional ethical committee and informed consents were obtained from all the patients and controls of the study group. Diagnosis of Parkinson disease done by physicians and confirmed by neurologist by using UK Parkinson's disease society brain bank clinical diagnostic criteria[6], with evidence on neurological examination has at least two of the three cardinal signs rest tremor, rigidity, bradykinesia.

Inclusion Criteria :

(1) Male and female patients diagnosed as Idiopathic Parkinson's disease aged between 50 to 70 years in the initial stage of disease (1-2 years) without any drug therapy.

(2) Willing to participate in study and provide informed consents.

(3) Control group included healthy volunteers who were consistent with the patients according to age, sex and body mass index.

Exclusion Criteria :

(1) Patients having blood disorders, obvious malignancy, hepatic, renal or cardiac disease and additional history of alcohol or smoking will be excluded from the study.

(2) Patients with coexisting neurological disorder like Alzheimer's disease, Stroke or any kind of neural deficit was also excluded.

(3) Patients on any concomitant medication such as Lipid lowering drug, antioxidants, vitamins, minerals, herbal treatment or the substance which may alter our study parameters excluded from study.

5 ml fasting blood samples from patients and controls were collected from anticubital vein, with all aseptic precaution. 2ml blood was collected in the heparinised vacutainers and remaining 3 ml blood was collected in plain vacutainers. Heparinised whole blood was used for the estimation of hemoglobin concentration by using commercial kits. Serum Iron and TIBC was measured using commercial kits by using the principle of Ferrozine/Magnsium Carbonate method. All the spectral analyses were carried out on fully automated UV-Visible spectrophotometer.

The statistical analysis was carried by Microsoft office Excel and SPSS software. Two tailed student 't' test was used for statistical analysis. The probability values $P<0.05$ was considered as significant and data were expressed in mean ±SD.

Observations

Table 1 — *Concentration of Blood Hemoglobin, Serum Iron and TIBC among Controls and patients with Parkinson's disease*

Parameters	Control (n = 52)	PD patients (n = 52)	p Value
Hemoglobin (g/dl)	14.36 ± 1.4	13.80 ± 1.5	p>0.05
Serum Iron (µg/dl)	137.30 ± 30.9	112.51 ± 30.3	p<0.001
Total Iron Binding capacity (µg/dl)	335.23 ± 45	305.88 ± 43.5	p<0.05

Discussion

As from our study we observed blood hemoglobin ($p>0.05$) levels were slightly less in PD patients but not shown any statistical difference as compared with control, it conclude that both PD patients and controls not suffered from any type of blood disorders. Further results shows, significant fall in serum Iron ($p<0.001$), TIBC ($p<0.05$) in PD patients as compared with controls, this might be due to dyshomeostasis of systemic iron metabolism in PD patients.

Cabera-valdiva, *et al* previously reported slight elevation in Serum Iron and Ferritin in PD compared with control[7]. G Logroscino, *et al*[8] and Abbot, *et al*[9] found significant reduction in Serum Iron, Ferritin and TIBC in patients of PD compared with control. Ferritin and TIBC are indirect measure of iron storage. As per our study Serum Iron and TIBC levels in PD patients were within normal range, but significantly lower than the controls.

Under normal conditions, iron status influences the synthesis of major proteins of systemic iron metabolism (eg Ferritin, Transferrin, Transferrin receptor). At the post transcriptional level cellular iron uptake regulated by cytoplasmic factors, the iron regulatory protein 1 and 2 (IRP1 and IRP2). When intracellular iron levels falls, IRPs bind to Iron-Responsive Elements (IREs) in the 5 – untranslated region of Ferritin mRNA and 3 – untranslated region of Transferrin receptor mRNA, inhibiting the translation of Ferritin RNA to decrease iron storage capacity and stimulates the translation of the Transferrin receptor mRNA by stabilization of mRNA to upregulate iron uptake. When sufficient intracellular iron is present the opposite situation develops to down-regulate intracellular iron storage[10].

So, normally during excess of iron load Ferritin synthesis get increased along with down regulating the synthesis of Transferrin receptor. But in Parkinson's disease though there is excess of iron deposited in various parts of brain, Ferritin levels remains low[5]. Normally, iron accumulates in substantia nigra with

increasing age. However, accumulation of iron in this region in PD far exceed compared with normal brain[11,12].

As per systemic iron metabolism whenever concentration of Ferritin is reduced, increased in Transferrin Receptors observed. Even though there are low Ferritin levels in PD, synthesis of Transferrin Receptor not increased, but it was observed to be decreased in PD affected brains as compared with control[12].

Faucheux, *et al* investigated alternative iron transport protein and found significant increase in lactoferrin receptor immunoreactivity in the mesencephalon, where the loss of dopamine neurons most severe. It is uncertain whether the increase in lactoferrin receptor activity in PD affected brain is result of local process or the effect of systemic defect in the regulation iron metabolism and storage. Because lactoferrin has a much higher affinity for iron than Tranferrin and transport of iron through lactoferrin receptor into dopaminergic neuron may be pathogenic. Moreover, increased lactoferrin receptor concentration over time might be responsible for the compartmental shift of iron stores from blood to substantia nigra[7,13].

As per our result, reduced Serum Iron concentration indicates decreased iron stores and then elevated levels of TIBC expected. However, significant lower concentration of TIBC observed in our study, which quite similar as per the observations concerning these proteins in the brains of patients with PD[5,12].

Abnormal regulation of iron proteins are a constant feature in PD affected brains. Liver is the site of synthesis of circulating iron proteins in the blood. Previous data and our results suggests defect in the overall system that regulate the synthesis of major proteins of iron metabolism in brain as well as in the liver of PD patients.

Alternatively, regulation of proteins involved in iron metabolism by the liver and brain may be independent but modified by similar pathogenic process involving IRE-IRP complexes or some other iron regulatory protein however to understand the biochemical mechanisms in elegant detail need further elucidations.

Conclusion

Liver is the site for the synthesis of iron circulating proteins in the blood. Previous results suggest about the existence of a defect in the system that regulates the synthesis of the major proteins of iron metabolism in the brain and our results suggesting the same circumstances occurred in the liver of Parkinson's disease patients. So, Parkinson's disease patients were fatalities of overall defect in systemic iron metabolism.

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