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Hyperhomocysteinemia- A Risk Factor for Parkinson Disease

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Summary:

Background: Increasing evidence suggests that elevated levels of serum homocysteine (Hcy) may be involved in several progressive neurodegenerative disorder including Parkinson Disease (PD).

Objective: To evaluate the association of elevated serum Homocysteine level in patients of Parkinson disease.

Methods: This case-control observational study was conducted in Neurology Department of Bangabandhu Sheikh Mujib Medical University (BSMMU) to determine the relation of increased level of serum homocysteine with patients of PD. In this study, serum level of homocysteine as well as folic acid and vitamin B12 were measured in patients suffering from parkinson disease (PD); and compared to age and sex matched control subjects.

Result: The results of the study showed that mean age of PD was 58.95±9.74 years. PD was more common in male (M:F = 1.6:1). Majority (55%) of the PD patients came from low middle class group. Mean duration of PD was 6.94±4.96 years and majority (42.5%) of PD patients were in stage II. We found significantly elevated concentrations of Hcy in PD patients (13.93±5.88 µmol/h) in comparison with control subjects (11.13±5.54 µmol/h), p=0.32. Longer duration of PD, advanced stage and reduced mini mental state examination (MMSE) score were also associated with increased level of serum homocysteine. Serum level of folic acid and vitamin B12 did not differ significantly between cases and controls, p=0.057; p=0.95 respectively.

Conclusion: This study showed significant association of elevated serum homocysteine in patients with PD. So our hypothetical conclusion is that hyperhomocysteinemia is a risk factor for PD.

Key words: Parkinson disease, Hyperhomocysteinemia, Risk factor.

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Introduction:

Parkinson disease (PD) is a progressive neurodegenerative disorder which involve dopaminergic neuron of substantia nigra. The number of dopaminergic neuron is reduced to 30% or less in PD patients[1]. It is diagnosed on the basis of characteristic motor disturbances (bradykinesia, resting tremor, rigidity and postural instability), asymmetrical symptom at onset and good response to levodopa[2]. PD is a multifactorial illness with likely genetic and environmental determinants[3]. Increasing age is the only definitive risk factor for Parkinson disease. The majority of new cases occur between ages of 50 and 70[4].

Risk factors for Parkinson disease include exposure to environmental toxin, genetic predisposition and possibly emotional stress[5]. It rarely occurs on a family basis. An increase in serum homocysteine levels in Parkinson disease recently has been observed[6,7].

Homocysteine is an amino acid arising by methylation of methionine that does not participate in the synthesis of protein and reconverted into methionine in presence of vitamin B12 and folate, into cysteine in presence of Vit B6[8].

The optimum serum Hcy level for healthy individuals are less than 9 µmol/L, while moderately and highly increased atherosclerosis risks are observed in the range of 9.1-15 µmol/L, and at values of more than 15 µmol/L respectively[9].

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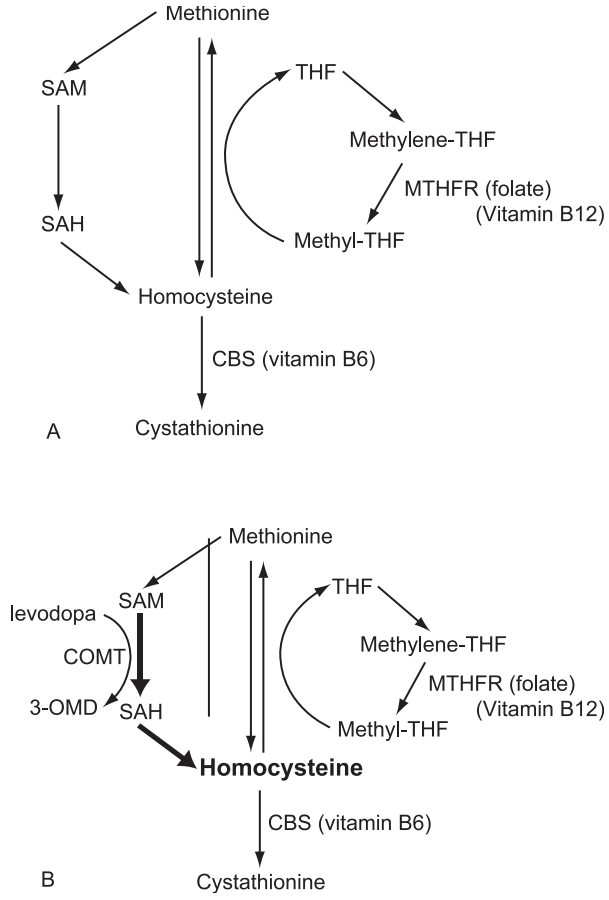

Fig: ***(A)*** *Shown is a simplified overview of homocys-teine metabolism.* ***(B)*** *Effect of L-dopa on the metabolism of homocysteine. Metabolism of L-dopa to 3-OMD causes an increase in the formation of SAH, which is immediately metabolized to homocysteine. Methylene THF = methylene tetrahydrofolate; MTHFR = methylenetetrahydrofolate reductase; SAM = S-adenosyl-methionine; SAH = S-adenosylhomocysteine; COMT = catechol-O-methyltransferase; 3-OMD = 3-O-methyldopa, CBS=cystathione beta synthase.*

Patients with Parkinson disease treated with L-dopa also exhibit 10-30% higher level of serum homocysteine[10,11].There are many possible causes of hyperhomocysteinemia: genetic factors, nutritional causes, systemic disorders, medication, as well as physiological and lifestyle factors. Recently it has received particular attention because of its association with pathogenesis of several neurological, cerebrovascular and cardiovascular disorders (e.g. Stroke, Alzheimer's disease, Vasular dementia, Ischaemic heart disease (IHD) and Parkinson disease[6,12]. The primary aim of this study was to evaluate a possible relationship between hyperhomocysteinemia, age, advanced stage, cognitive dysfunction and increased duration of Parkinson disease. Because some studies have shown that homocysteine in PD may be influenced by vitamin B12 and folic acid[10,14], serum level of vitamin B12 and folic acid were also measured.

Materials and method:

This study was case control study conducted in Department of Neurology, BSMMU from January 2010 to December 2011. Forty cases and forty controls were selected randomly following some inclusion and exclusion criteria. Cases were patient with PD who presented with two of four cardinal signs: resting tremor, bradykinesia, rigidity and postural instability; and aged 45 years or above of both sexes. Controls were age and sex matched healthy people, patients other than PD, parkinsonism, IHD, diabetes mellitus, ischaemic stroke and non smokers.

The variables included in the study were age, sex, educational status, socio-economic status, MMSE score, duration and stage of PD. Detailed history taking and clinical examination were done. Serum homocystine (Hcy), vitamin B12 and folate were measured. Data were analyzed with the help of computer using SPSS (statistical package for social science). Statistical significance was set at 0.05 level and confidence interval at 95%.

Results:

Total forty patients of parkinson disease (PD) from the department of Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU) were taken as case along with forty age and sex matched control subjects. Table I showed age distribution of PD patients, were mean age was 58.95±7.94 years with range from 45 to 79 years. Sixty percent of PD patients were male and forty percent were female; male to female ratio was 1.6%.

Table II showed mean systolic blood pressure of study patients which was 129.87±15.4 mm of Hg and mean diastolic blood pressure 80±10.65 mm of Hg. Mean duration of PD was 6.94±4.96 years and mean duration of antiparkinsonian drugs was 5.13±4.29 years. It was observed that mean mini mental stat examination (MMSE) score was 24.75±3.06. Mean serum homocysteine was 13.93±5.88 µ mol/L, mean serum vit B12 level was 416.53±240.4 p gm/ml and mean serum folate level was 9.46±2.96 ng/ml.

Table-I

Age distribution of the study patients (n=80)

Age (in the year)	Case (n=40)		Control (n=40)		P value
	N	%	n	%	
41-50	14	35.0	10	25.0	
51-60	9	22.5	9	22.5	
61-70	13	32.5	12	30.0	
>70	4	10.0	9	22.5	
Mean ± SD	58.95	±9.74	62.15	±11.08	0.174^{ns}
Range	(45	-79)	(46	-85)	

t value=-1.37, df-74; P value reached from unpaired t-test

Table-II

Demographic, clinical features and serum homocysteine, B12 and folate levels in case (PD) and control.

	Case (PD patient) (n=40)	Control (PD patient) (n=40)	P value
Age in years	58.95±9.74	62.45±11.08	0.174
Sex (M/F)	24/16	25/15	0.818
Blood pressure (mm of Hg)	SBP- 129.87±15.4 DBP- 80±10.65	SBP- 129.63±15.25 DBP 79.75±9.54	.944.912
Duration of PD (years)	6.94±4.96		
Duration of antiparkinsonian drugs (years)	5.13±4.29		
MMSE score	24.75±3.06	26.73±2.65	0.003
Serum Hcy (µmol/L)	13.93±5.88	11.13±5.54	0.032
Serum vit B12 (p gm/ml)	416.53±240.4	514.3±276.27	0.095
Serum folate (ng/ml)	9.46±2.96	7.82±4.47	0.057

Table III showed distribution of study patients according to stage of PD where majority of the patients were in stage II and stage III. From Table IV it was observed that serum homocysteine level were higher with increasing duration of PD. During 1-4 yeas mean serum homocysteine level was 11.64±3.27 µ mol/L and over 10 years was 18.7±6.02 µ mol/L. Table V showed that progressive increase of serum homocysteine level with progression of PD where mean serum homocysteine level in stage I was 8.52±2.23 µ mol/L and 27.57 µ mol/L in stage IV. Figure 1 showed significant positive correlation (r=0.4244; p=0.006) between serum homocysteine and age of PD patients. Figure 2 showed significant positive correlation (r=0.459; p=0.004) between serum homocysteine with duration of PD. Figure 3 observed significant positive correlation

Table-III

Distribution of the patients according to stage of PD (n=40)

Stage of Parkinson disease	Number of patients	Percentage
Stage I	9	22.5
Stage II	17	42.5
Stage III	13	32.5
Stage IV	1	2.5

Table-IV

Mean serum homocysteine level (mmol/L) according to duration of PD (n=40)

Duration of PD in years	Serum homocysteine (mmol/L) Mean±SD
1 – 4	11.64±3.27
5 – 9	14.12±5.54
≥10	18.7 ±6.02

(r=0.663; p=0.001) between serum homocysteine with stage of PD and figure 4 showed significant negative correlation (r=0.7978; p=0.001) between serum homocysteine and mini mental state examination score (MMSE) in PD patients.

Table-V

Mean serum homocysteine level (mmol/L) according to stage of PD (n=40)

Stage of PD	Serum homocysteine (mmol/L) Mean±SD
Stage I	8.52±2.23
Stage II	12.58±4.00
Stage III	17.67±5.83
Stage IV	27.57±0.0

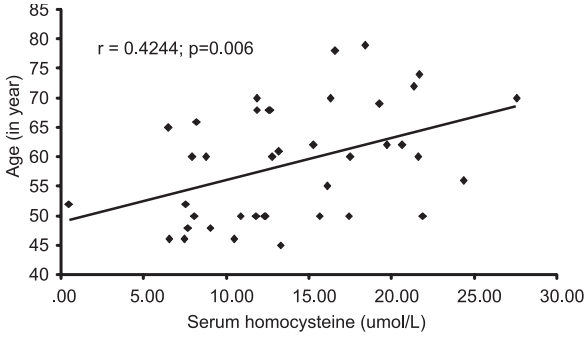

Fig. 1: *Scatter diagram showing the significant positive correlation (r=0.4244; p=0.006) between serum homocysteine and age of PD patients (case).*

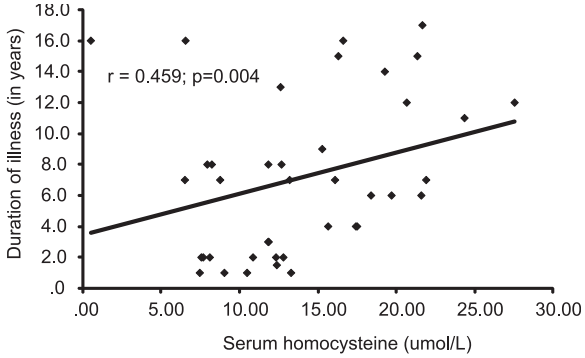

Fig. 2: *Scatter diagram showing the significant positive correlation (r=0.459; p=0.004) between serum homocysteine with duration of PD (in years).*

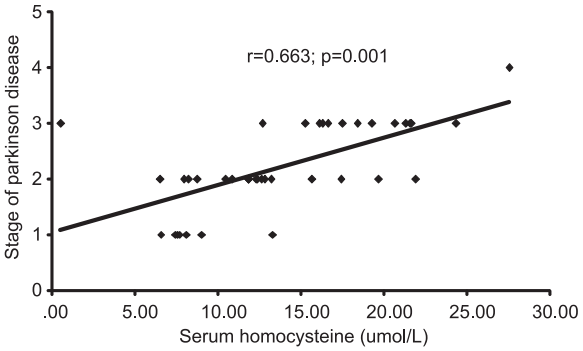

Fig. 3: *Scatter diagram showing the significant positive correlation (r=0.663; p=0.001) between serum homocysteine with stage of Parkinson disease.*

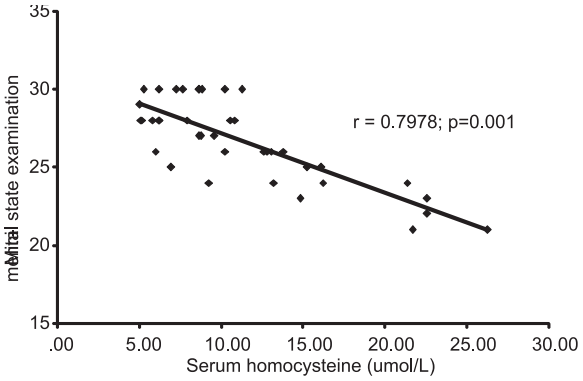

Fig. 4: *Scatter diagram showing the significant negative correlation (r=-0.7978; p=0.001) between serum homocysteine with mini-mental state examination score in PD patients (case).*

Discussion:

Hyperhomocysteinemia has been found to be an important risk factor for parkinson disease[8]. It is also a risk factor for several neurological, cerebrovascular and cardiovascular disorders (e.g. Stroke, Alzheimer disease, Vascular dementia, IHD[12,13,15]. This present study was conducted to see the association of elevated serum Hcy with patients of PD. The results showed that mean age of PD was 58.95±9.74 years. Previous studies showed that mean age of PD patients was 66.29±7.69 years[8], 60.83±13.13 years[16]. Most of the PD patients in this study belonged to 5th and 6th decade (57.5%). Mean age of PD was lower than that of previous studies which can be explained by increased life expectancy in those areas. Male to female ratio of cases were 1.6:1 which reflected the findings of previous studies[6,16].

Fifty five percent of PD patients in this study came from low income socioeconomic status, however hospital based study may not reflect association of socioeconomic status with parkinson disease.

In this present study, educational status of majority patients were primary level 37.5% in cases and 45% in controls; mean systolic blood pressure in case group was 129.87±15.84 mm of Hg, mean diastolic blood pressure was 80±10.6 mm of Hg with no significant difference (P>0.05) between case and control.

The mean duration of illness in case group was 6.94±4.96 years with range from 1 to 17 years; mean duration of anti-parkinsonian drugs was 5.13±4.29 years with range from 0 to 15 years. Majority of patients with PD had stage II disease (42.5%) i.e. in early stage .

Memory impairment (i.e. reduced MMSE score) was found in 35% of PD patients whereas only 6% in controls and the differences was statistically significant (P<0.05) between two groups in chi-square test. The mean mini-mental state examination (MMSE) score was 24.76±3.06 in PD patients with range from 18 to 29 and 26.73±2.65 with range from 21 to 30 in control subjects, the difference was statistically significant (P=0.003) between two groups in unpaired t-test. The study also showed significant negative correlation between serum Hcy and MMSE score in PD patients (Fig. 4). Present study finding was consistent with previous study, a multicentric cross-sectional study conducted where Hcy levels were higher in PD patients compared to controls (17.5µmol/L ±10.2 vs 11±4.1; P<0.00001). Among patients with PD, Hcy levels were higher in PD patients with dementia group compared to PD patients without dementia group (20.7±12.1µmol/L vs 15.8±8.5µmol/L with P value <0.002)[6].

The vitamin B12 and folic acid serum concentration did not differ significantly between the patient and control subject; p value 0.095 and 0.057 respectively. This finding was in agreement with previous finding[6].

Hcy measurements in serum showed that control subjects had a mean level of 11.13±5.54µmol/L with range from 5 to 26.3µmol/L. PD patients showed significantly increased concentration of Hcy (13.93±5.88µmmol/L) in comparison with the control subjects (P<0.05). Besides this there were significant positive correlation of raised serum homocysteine with advancing age (r=0.42; P=0.006), this finding supports the findings of previous studies which observed significant positive association between serum homocysteine and PD patient where patient had serum Hcy level 17.3±6.2µmol/L in comparison to 13.55±3.9 in control subject with 95% CI 0.11[9]. This association was also found in another study, where Hcy level was elevated (PD 15.1µmol/L and control 11.2µmol/L)[8]. On the other hand, it was found that serum homocysteine level was 13.13±4.25µmol/L in control, 16.93±7.08 in PD patients without levodopa treatment and 17.05±6.25 in PD patients with levodopa[16].

The present study showed that there was significant positive correlation of elevated serum Hcy with the increased duration of PD (r=0.46; P=0.004). Moreover there was significant positive correlation between raised serum Hcy with advanced stage of PD (r=0.66; P=0.001).

Several studies showed that elevated levels of Hcy in PD are related to levodopa treatment[6,16,17]. Further studies are needed to determine if such elevation occurred with levodopa can also be found in patients of PD treated with other antiparkinsonian drugs e.g. dopamine agonist, Catechol-O-Methyl-Transferase (COMT) inhibitors.

Although vitamin levels (Vitamin B12 and folic acid) were normal in PD, vitamin supplementation with vitamin B12, folic acid and pyridoxin, might lead to normal Hcy levels[9]. Further studies are needed to investigate whether vitamin treatment might be able to reduce elevated Hcy levels in PD and other neurodegenerative disorders. A meta-analysis had found that an 11% reduction in stroke and coronary artery disease with each 3µmmol/L reduction in serum homocysteine[18].

Another randomized clinical trial has been published, which demonstrated that vitamin supplementation (with folate, vitamin B6 and B12) after coronary angioplasty reduced the rate of restenosis requiring revascularization by 39%[19]. Large scale clinical trials of folate supplementation also have been launched e.g. vitamin intervention for stroke prevention, vitamins to prevent stroke[20,21]. Such randomized large scale clinical trial may be undertaken to see whether reduction of serum homocysteine level with these vitamins can reduce the

progression of PD and prevent deterioration of cognitive impairment in patients with PD.

So, in this present case-control study, we found a significant association of elevated serum Hcy level in PD patients in comparison with the corresponding controls. Memory impairment, advanced stage of PD and increased duration of illness were also associated with raised serum Hcy levels.

Conclusion:

The aim of this present case-control study was to explore the association of elevated serum homocysteine with patients of Parkinson disease, which showed a significant association. In addition, elevated serum homocysteine had significant association with advance stage of disease, increase duration of PD and cognitive impairment. So our hypothetical conclusion is that elevated serum homocysteine level might be a risk factor in the pathogenesis of Parkinson disease.

Limitation:

Our study had a number of limitations: (i) Small size of study sample. However we were able to describe a significant association between high serum homocysteine level and Parkinson disease. (ii) We excluded stroke only based on clinical information as cerebral imaging was not included in our protocol. (iii) Our data were based on a single measurement of Hcy levels and this could have underestimated the association between the Hcy level and PD of about 10-15%[22]. (iv) Cognitive function in our patients was assessed only by MMSE which had several limitations as a scoring instrument for dementia. (v) Our study design did not allow to determine whether antiparkinsonian drugs were responsible for elevated serum homocysteine levels as patient received various combination of antiparkinsonian drugs. Furthermore (vi) many confounding variables like age, sex, dietary habit may influence the result of the study.

In order to establish the association of raised serum Hcy with Parkinson disease it will require a worldwide multicentre large scale study. But such an extensive study was not feasible for several constraints like time, resources and financial problem.

Recommendation:

Parkinson disease is a progressive neurodegenerative disorder of unknown etiology. No treatment is available currently to cure or to prevent progression of the disorder. Treatments are available only to alleviate symptoms and their cost is very high which need to be continued for life long. If our hypothetical conclusion of elevated serum homocysteine is proved by large scale multicentre study, further clinical trial of lowering elevated serum homocysteine with supplementary vitamin B12, pyridoxine and folic acid may be conducted to see their effect on halting or delaying progression of this disorder. Positive outcome of such intervention will bring significant improvement in the management of PD and halting or delaying progression of this progressive neurodegenerative disorder.

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