Original Article

Study of Prevalence of Vitamin B12 Deficiency and Hyperhomocysteinemia in Patients of Deep Vein Thrombosis

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Background : Common condition encountered by surgeons are Pulmonary Embolism (PE) and Deep Venous Thrombosis (DVT). About one-third of individuals with symptomatic Venous thromboembolism have PE, whereas the remaining two-thirds exhibit DVT alone.

Aims and Objective : To assess the Serum homocysteine & serum Vitamin B12 levels in patients with DVT and to examine the influence of various risk factors on serum homocysteine levels and serum Vitamin B12 levels.

Material and Methods : It is a retrospective study conducted in Department of General Surgery, BJ Medical College and Civil Hospital, Ahmedabad from May, 2017 to September, 2018 including 20 Patients. Patients having a DVT diagnosis older than five years were included.

Results : Out of 20 patients, Hyperhomocysteinemia was present in 8(40%) and Vitamin B12 Deficiency in 9 (45%) patients. The mean age was 34.6 years & only one female patient (5%). Immobility was present in 6(30%), Smoking history in 8(40%), Cardiac Co-morbidity in 4(20%) Patients.

Conclusion : Hyperhomocysteinemia & Vitamin B12 Deficiency are potentially modifiable risk factors that must be considered when evaluating patients for DVT.

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Key words **: Deep Vein Thrombosis, Hyperhomocysteinemia, Vitamin B12 Deficiency.**

The development of a semisolid coagulum inside the venous system is known as venous thrombosis, which may affect the superficial system (often referred to as superficial thrombophlebitis) or the Deep Venous Thrombosis (DVT)[1].

According to estimates, the prevalence of DVT in the general population ranges from 80 to 100 per 100,000 yearly in western countries to 4-75 per 100,000 in South Asia[2]. Swelling and pain, particularly in the calf, are the most typical symptoms of a Deep Vein Thrombosis, which often affects one lower limb. Nevertheless, bilateral Deep Vein Thrombosis is frequent, occurring in up to 30% of cases.

The objective of the present research is to assess the Serum Homocysteine & Serum Vitamin B12 levels in patients with DVT and to examine the influence of various risk factors on serum homocysteine levels and serum Vitamin B12 levels (Fig 1).

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Editor's Comment :

- In Indian Scenario, in patients of Deep Vein Thrombosis, folic acid, pyridoxine and cyanocobalamin supplementation has shown significant reduction in incidences of Thrombosis.

Treatment for hyperhomocysteinemia depends on the underlying reason; however, Vitamin supplementation (with Vitamin B12, pyridoxine, and folic acid) is often successful in lowering homocysteine levels.

A ruptured Baker's cyst, arterial ischaemia,a thrombosed popliteal aneurysm,a ruptured plantaris muscle and a calf muscle haematoma are among the potential diagnoses for a DVT (Figs 2&3).

Pathophysiology :

There are a number of acquired risk factors for DVT, like surgery, cancer/cancer treatment or pregnancy, as well as genetic risk factors, like defects in protein C, protein S and antithrombin. Moreover, adaptable risk factors like hyperhomocysteinemia and obesity are notable from a preventative perspective.

There are multiple causes of hyperhomocysteinemia, such as vitamin deficiency (Vitamins B12, B6 and Folate), renal failure and many drugs, such as anticonvulsants and antihyperlipidemics, as well as physiological factors like advancing age or male gender, MTHFR gene polymorphism[3].

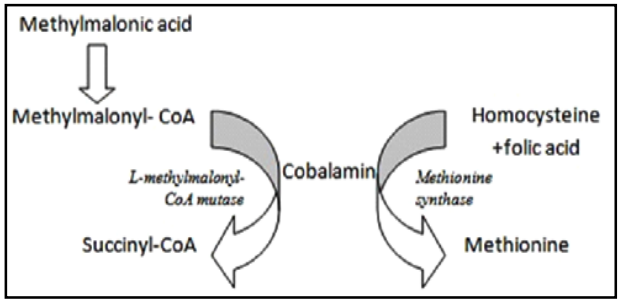

Fig 1 — Conversion of Homocysteine to Methionine

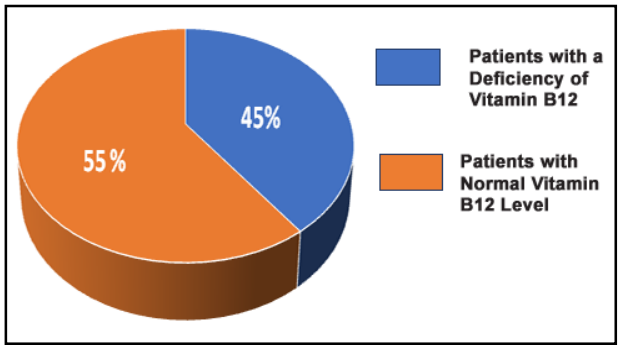

Fig 2 — Percentage of patients with Vitamin B12 Deficiency

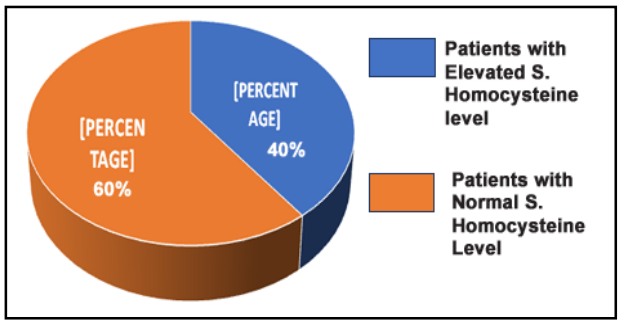

Fig 3 — Percentage of patients with Hyperhomocysteinemia

Vitamin B12 deficiencies are a common problem Worldwide. Chronic gastritis,Atrophic gastritis, Pernicious anaemia, Sjögren's syndrome, Vegetarianism, older people and chronic alcoholism, *Helicobacter pylori*-related gastritis, ileal resection and Post-gastrectomy, chronic pancreatic exocrine insufficiency, Crohn's disease, Small intestinal bacterial overgrowth, achlorhydria and coeliac disease, Oral contraceptive, Transcobalamin II deficiency, Drugs Metformin, hormone replacement therapy and pregnancy,histamine H2-receptor antagonists and proton pump inhibitors[4].

The three elements identified by Virchow more than a century ago continue to have a role in the onset of venous thrombosis. These are :

- blood contact with an abnormal surface (like endothelial damage);
- abnormal flow (such as stasis);
- abnormal blood (like thrombophilia).

Homocysteine is a sulphur-containing "amino acid" that is generated from the necessary amino acid methionine by demethylation.

In the above diagram, there is a requirement of Cobalmin& folic acid for the conversion of Homocysteine into methionine, in deficiency of Vitamin B12 & Folic acid, there is elevated Homocysteine which carries atherogenic propensity as a consequence of endothelial dysfunction and damage caused thrombus formation and platelet activation. Smooth muscle hypertrophy, elastic lamina degradation and Intimal thickening are three of the main processes of homocysteine-induced vascular injury.

The thrombus begins as a platelet cluster. The lumen of the vein wall is eventually blocked by a mesh made of fibrin and red blood cells. The coralline thrombus eventually develops into a loose red fibrin clot with many red blood cells. The clot may break off and travel as a pulmonary embolus to the lung since it is likely to continue up to the next big venous branch[3].

Homocysteine concentrations may be decreased by Folic acid alone or in combination with Vitamins B6 and B12. Normal plasma homocysteine levels return 4 to 6 weeks after starting medication, although they might return as soon as two weeks later[5].

Materials and Methods

This Retrospective Observational study was conducted in Department of General surgery, B J Medical College and Civil Hospital, Ahmedabad from May, 2017 to September, 2018 including 20 Patients.

DVT diagnoses in patients older than five years were included.

Exclusion Criteria :

- Patients with concurrent medication use (such as thiazide diuretics, isoniazide, carbamazepine, penicillamine, niacine, theophylline, L-Dopa, hormone replacement therapy, antiepileptics, Vitamin B12 and B6 antagonists, phenytoin, methotrexate) or conditions that could affect the blood level of homocysteine should be particularly careful.
- many co-morbidities (ie, hypothyroidism)
- inflammatory Bowel diseases and pernicious anaemia diseases
- respiratory insufficiency
- Sepsis was thoroughly eliminated from the research.

Demographic information, signs and results and the background of potential risk factors for Deep Vein

Thrombosis were noted. Deep venous "Doppler Ultrasonography" of the extremities is used to identify DVT.

Blood investigations (CBC, RFT, LFT, APTT, PT-INR), S Lipid Profile, S Vitamin B12, Serum. Homocysteine Electrocardiography, Chest X-ray, Echocardiography and screening of USG Abdomen-Pelvis were done. Kang, *et al* have categorized hyperhomocysteinemia as moderate (homocysteine concentration 15-30 mmol/litre), intermediate (greater than 30 to 100 mmol/litre) and severe (greater than 100 mmol/litre) based on concentrations obtained in fasting[3] (Tables 1&2).

Results

An overall of twenty patients with a mean age of 34.6 years who satisfied the inclusion criteria throughout the course of 16 months was engaged in the research.

Risk factors for the expansion of DVT were assessed. Detected risk factors were examined in 6 participants with DVT, 5 Patients had Surgery, and 1 Patient had Trauma.

Patients were treated with Standard treatment protocol Injection Unfractionated heparin 5000 IU/8 hourly for days and overlapped Tablet warfarin 5 mg once a day on the 4th day, continued for 6 months.

Regular Prothrombin Time-International Normalized Ratio was done.

Moderate Hyperhomocysteinemia in 4 Patients and intermediate Hyperhomocysteinemia in 4 patients was diagnosed. Nobody of the patients had a severe case of homocysteinemia.

A deficiency of Vitamin B12 was found in 9 (45%) patients.

Table 1 — *Comparative Studies*

	Present Study	Kamat, *et al*[7]	Kokturk, *et al*[8]
Males	95%	75%	39%
Females	5%	25%	61%
Immobility	30%	5.71%	29%
Diabetes Mellitus	10%	41.43%	17%
Hypertension	5%	37.14%	29%
Hyperhomocysteinemia	40%	31.42%	63%

Table 2 — *Various Parameters*

Parameters	Patient (n=20)
Age (Mean)	34.6 years
Sex (Female), n (%)	1 (5 %)
Symptoms at admission :	
Pain, n (%)	16 (80%)
Swelling, n (%)	4 (20%)
Pain and Swelling both, n (%)	16 (80%)
Fever, n (%)	2 (10%)
Immobility	6 (30%)
Smoking History, n (%)	8 (40%)
Systemic hypertension, n (%)	1 (5%)
Diabetes mellitus, n (%)	2 (10%)
Cardiac comorbidity, n (%)	4 (20%)
Serum urea, n (%)	1 (5%)
Total cholesterol, mg/dL n (%)	4 (20%)
Echocardiography, n (%)	4 (20%)
USG Abdomen-Pelvis, n (%)	1 (5%)
Upper-Limb Involvement, n (%)	2 (10%)
Elevated Serum Homocysteine, n (%)	8 (40%)
Vitamin B12 Deficiency, n (%)	9 (45%)

Discussion

In our study, there is a 40% prevalence of Hyperhomocysteinemia & 45% Prevalence of Vitamin B12 Deficiency out of 20 patients with DVT.

The mean serum Homocysteine level was 19.67 micromol/L and the average serum Vitamin B12 level was 345.35 pg/ml.

The baseline demographical characteristics, risk factors, clinical signs and laboratory results of the patients with DVT were similar when compared based on the prevalence of Hyperhomocysteinemia with the exception of total cholesterol levels, which were considerably greater and Vitamin B12 levels, which were substantially lower in patients with "Hyperhomocysteinemia".

Evidence for elastic lamina injury, intimal thickening and smooth muscle hypertrophy as one of the main processes of Homocysteine-induced vascular injury is rapidly emerging.

A further meta-analysis of twenty prospective trials observed that a 5-mmol per L rise in overall plasma homocysteine was linked to a 32% rise in the likelihood of developing ischemic heart illness and a 59% rise in the likelihood of suffering a stroke[3].

Although the exact processes behind this impact of homocysteine are yet unknown, the greatest evidence points to the involvement of oxidative stress and impaired nitric oxide.

Hyperhomocysteinemia and Vitamin B12 Deficiency are two clinically significant risk factors for venous thromboembolism that are considered to be modifiable. Normal levels vary greatly between different groups owing to the unique lifestyle variables that impact levels of plasma homocysteine, like nutrition, coffee use and smoking history.

According to Venous thromboembolism is independently correlated with Hyperhomocysteinemia and low Vitamin B levels: findings from the study of EDITH: Low serum folic acid and low Vitamin B12 levels have been found to be independently related with

venous thromboembolism in a hospital-based case-control analysis. However, the connection between low Vitamin B12 or low serum folic acid levels and venous thromboembolism is not entirely mediated by increased serum homocysteine[6].

Another previously mentioned risk factor for Hyperhomocysteinemia is growing older. Additionally, a number of lifestyle variables, including exercise, coffee use, protein intake and alcohol use which were not specifically examined in the research, could contribute to elevated Homocysteine levels.

Conclusion

The standard therapy for "Hyperhomocysteinemia" is folate supplementation, often with vitamin B12/B6. Hyperhomocysteinemia & Vitamin B12 deficiency is potentially modifiable risk factors that must be considered when evaluating patients for DVT. A large sample size is needed to study the prevalence of Vitamin B12 deficiency and Hyperhomocysteinemia.

Conflict of Interest : None

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