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Prevalence of Hyperhomocysteinemia in Patients with Venous Thromboembolism in Tan Tock Seng Hospital, Singapore

Lee YE[1], Kng KK[1] and Sule AA[2*]

[1]Department of Pharmacy, Tan Tock Seng Hospital, Singapore

[2]Department of General Medicine, Tan Tock Seng Hospital, Singapore

[*]Corresponding author:

Ashish Anil Sule,
Department of General Medicine, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, 308433, Singapore

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Keywords:

Hyperhomocysteinemia; Deep vein thrombosis; Pulmonary embolism; Venous thromboembolism; Risk factor

1. Abstract

1.1. Introduction: Venous thromboembolism (VTE) is the third leading vascular diagnosis after acute coronary syndrome and stroke. Risk factors for VTE include hyperhomocysteinemia and others. This study aims to determine the prevalence of hyperhomocysteinemia in patients with VTE in Tan Tock Seng Hospital (TTSH) and its associated risk factors.

1.2. Methods: This is a retrospective, cross-sectional study. Patients ≥ 21-year-old with homocysteine levels >15 µmol/L, admitted for VTE from 1st January 2010 to 30th June 2020, were included. Demographics, medical history and concurrent medications were also collected.

1.3. Results: Sixty-two patients were included. There were 32 (52%) female and the mean age was 58. Thirty-six (58%) patients were Chinese. Prevalence of hyperhomocysteinemia in patients with VTE was 31%. Incidence of deep vein thrombosis (DVT), pulmonary embolism (PE) and cerebral venous thrombosis in these patients was 53%, 66% and 11%, respectively. Besides osteoporosis and rheumatoid arthritis, other parameters did not influence the incidence of VTE occurrence.

1.4. Conclusion: Prevalence of hyperhomocysteinemia in patients with VTE in TTSH appears to be higher than that previously reported. Hyperhomocysteinemia may be the most likely factor. Other possible causes may be due to association with osteoporosis and rheumatoid arthritis.

2. Introduction

Venous thromboembolism (VTE) occurs when there is a blood clot in the veins and can be classified as deep vein thrombosis (DVT) or pulmonary embolism (PE). In a 2006 study done by Spencer et al, VTE was the third leading diagnosis after acute coronary syndrome and stroke [1]. In the western populations, VTE is estimated to affect approximately 1 per 1000 persons per annum [2]. The incidence of VTE was thought to be low amongst Asian population until recent studies reveals rates of 15-20% that of western populations [3]. Risk factors identified for VTE include increasing age, immobility, malignancy, certain drug use, hereditary thrombophilia as well as hyperhomocysteinemia [4, 5].

Homocysteine is an amino acid that is absent in the natural diet and contains the sulfur element [6]. It is formed intracellularly during the metabolism of methionine, an essential amino acid, in a demethylation process. The metabolism process involves the presence of B vitamins, pyridoxine (B6), cyanocobalamin (B12), and folate (B9) as the main cofactors [7, 8]. Therefore, factors that compromise the availability of these vitamins are bound to destabilize homocysteine metabolism.

The acceptable ranges for homocysteine in the bloodstream are between 5 µmol/L and 15 µmol/L [9]. Hyperhomocysteinemia refers to plasma levels of homocysteine higher than 15 µmol/L and is associated with atherosclerosis and vascular thrombosis [10]. It can be categorized as moderate (15-30 µmol/L), intermediate (30-100 µmol/L) or severe (>100 µmol/L). Prevalence of hyperhomocysteinemia varies, with reports of 20-60% depending on age, gender, ethnicity, comorbidities and geographical location [8, 11-14]. Hyperhomocysteinemia can be caused by renal failure, drugs (such as anticonvulsants and cholesterol-lowering drugs)

as well as deficiencies in vitamins like pyridoxine, folic acid, or cyanocobalamin [15, 16].

The link between hyperhomocysteinemia and venous thromboembolism remains controversial [17]. The primary objective of this study was to determine the prevalence of hyperhomocysteinemia in patients with VTE in Tan Tock Seng Hospital. The secondary objective was to identify the risk factors of patients which were associated with hyperhomocysteinemia and VTE.

3. Methods

This is a retrospective, cross-sectional study conducted at Tan Tock Seng Hospital. Patients were eligible if they were 21 years old and above and admitted for VTE with homocysteine levels done during their admission between 1st January 2010 and 30th June 2020. Patients who were pregnant or breastfeeding were excluded. The categories of data collected included demographic data, embolism-related disorders, laboratory results for both serum homocysteine and creatinine, relevant medical conditions, medications and supplements that the patient could be taking.

Data was extracted from the healthcare intelligence system in Tan Tock Seng Hospital. This study was approved by the Institutional Review Board (IRB) of National Healthcare Group.

4. Statistical Analysis

Descriptive statistics were carried out on the patient demographics. Patients who were admitted for VTE with homocysteine levels >15μmol/L were analyzed. The spearman's correlation test was used to assess the relationship between homocysteine levels, age and serum creatinine. The Wilcoxon rank sum test and Kruskal-wallis test were used to determine risk factors associated with hyperhomocysteinemia and VTE. Statistical significance was defined as $p<0.05$. All statistical tests were carried out using SPSS version 28.0.

5. Results

The demographic characteristics of the recruited patients were summarized in Table 1. There were slightly more females (N = 32, 52%) than males (N = 30, 48%). Ethnically, the majority were Chinese (N = 36, 58%). The mean age was 58 with a standard deviation of 17.6 (Minimum = 22 years, Maximum = 89 years) and majority were less than 65 years old (N = 40, 65%). Almost half of the patients were non-smokers (N = 30, 48%).

Between 1st January 2010 and 30th June 2020, 5139 patients were admitted for VTE. Of the patients with homocysteine levels done, the prevalence of hyperhomocysteinemia was 31%. The homocysteine levels amongst the patients range from 16 μmol/L to >50 μmol/L. The mean homocysteine level was 23 μmol/L (female: 23 μmol/L, male: 21 μmol/L).

Regarding types of VTE, more than half of the patients had either pulmonary embolism or deep vein thrombosis at 66% and 53%, respectively. A quarter of the patients had recurrent VTE.

In terms of thrombophilia screen, less than a quarter of the patients had abnormal results, with protein S deficiency being the most frequent (N = 9, 15%). None of the patients had antiphospholipid antibodies.

Certain chronic conditions that require prolonged pharmacological management are also likely to be associated with elevated blood levels of homocysteine [16, 18]. Those frequently encountered conditions which were evaluated were summarized in Table 2. The most prevalent condition found in our patients was diabetes (N = 18, 29%), while none of the patients had a history of pernicious anemia.

A proportion of the patients evaluated were prescribed with Vitamin B supplements. Amongst medications that might influence homocysteine levels, Metformin had the highest frequency of 15% (N = 9) followed by Fenofibrate and Methotrexate at 8% (N = 5) each.

Spearman's rank correlation was carried out to test the relationship between homocysteine levels, age and serum creatinine (Table 3). No statistical significance was observed. Wilcoxon rank sum test showed statistical significance between homocysteine level and osteoporosis as well as homocysteine level and rheumatoid arthritis ($p = 0.040$ and $p = 0.035$, respectively) (Table 4). Other medical conditions, prescribed medication, vitamin supplements, genetic problems and demographic factors were not found to have any statistically significant influence on the elevated plasma homocysteine level (Tables 4 to 6).

6. Discussion

Varying prevalence for hyperhomocysteinemia had been reported. A systemic review and meta-analysis by Yang BY et al reported an average prevalence of 27.5% in China but it was not clearly stated what comorbidities the study participants had [11]. The study showed that the prevalence of hyperhomocysteinemia was higher in males and elderly as well as those staying in the Northern regions. A population based cross-sectional study done in Chinese patients and compared those with and without hypertension by Yang Y et al reported a prevalence of 35.4% [12]. Another study done in Chinese patients with hypertension by Wang et al reported a prevalence of 51.6% [13].

From our results, the mean homocysteine level amongst the patients was 23μmol/L (female: 23μmol/L, male: 21μmol/L). The prevalence of hyperhomocysteinemia amongst patients admitted for VTE between 1st January 2010 and 30th June 2020 was 31%. It appeared that in general, the prevalence of hyperhomocysteinemia seems to differ, depending on the study population.

An overview of hyperhomocysteinemia and thrombosis by Eldibany et al stated that men, smokers and increasing age were factors that influenced plasma homocysteine levels [19]. This observation was also seen in the study by Yang BY et al and The Hordaland Homocysteine Study by Refsum et al [11, 14]. Contrary to these

studies, our study found a higher prevalence of hyperhomocysteinemia in women and non-smokers, while age did not seem to influence the homocysteine levels. Homocysteine level was also not affected by ethnicity. Hence, hyperhomocysteinemia may be the only likely factor to cause VTE in these patients.

Hyperhomocysteinemia had been shown to inhibit bone formation by increasing the activity of osteoclast and may contribute to osteoporosis [20]. van Meurs et al found that increase in homocysteine levels was associated with increased risk of osteoporotic fractures in the elderly regardless of their bone mineral density or other risk factors [21]. Based on our results, elevated homocysteine level was also associated with osteoporosis ($z = -2.057$, $p = 0.040$). Fractures and immobility are known risk factors for VTE [22]. Whether the correction of hyperhomocysteinemia can reduce osteoporosis and hence risk of fractures and immobility needs to be further determined.

A meta-analysis by Hu LJ et al demonstrated increased odds of 2.23 for developing VTE in patients with rheumatoid arthritis [23]. Kim SC et al showed an increased risk of hospitalization due to VTE in rheumatoid arthritis patients started with a biologic disease-modifying antirheumatic drug (DMARD) compared to those who were started on a non-biologic DMARD or methotrexate [24]. Also, high homocysteine levels was found to be predictive of atherothrombotic events in patients with rheumatoid arthritis in the study by Berglund S et al [25]. These findings were reflected in our results as well, whereby VTE patients with hyperhomocysteinemia was associated with rheumatoid arthritis ($z = -2.103$, $p = 0.035$) while methotrexate use was not ($z = -1.752$, $p = 0.080$).

7. Limitations

The main limitation of this study is that it is a retrospective study. However, homocysteinemia and VTE is not common. Hence, retrospective data would give us immense value. It also tells us the prevalence of homocysteine in Asian population and if it is associated with VTE in specific group of population. Another limitation is the lack of comparison between patients with elevated homocysteine levels and normal homocysteine leveels.

8. Conclusion

The prevalence of hyperhomocysteinemia in patients with VTE in Tan Tock Seng Hospital was 31% which appears to be higher than that previously reported. From our findings, hyperhomocysteinemia may be the most likely factor to cause VTE in these patients. Other possible causes of VTE for our patients with hyperhomocysteinemia may be due to association with osteoporosis and rheumatoid arthritis.

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Table 1: Demographic characteristics, types of venous thromboembolism and related genetic conditions

Variable	Category	Sample (N = 62)	Percentage (%)
Gender	Male	30	48
	Female	32	52
Age	< 65 years old	40	65
	≥ 65 years old	22	35
Ethnicity	Chinese	36	58
	Malay	11	18
	Indian	9	14
	Others	6	10
Smoking status	Smoker	11	18
	Non-smoker	30	48
	Unknown	19	31
	Ex-smoker	2	3
Deep vein thrombosis	Yes	33	53
	No	29	47
Pulmonary embolism	Yes	41	66
	No	21	34
Cerebral venous thrombosis	Yes	7	11
	No	55	89
Recurrent venous thromboembolsim	Yes	15	24
	No	47	76
Factor V Leiden mutation	Yes	1	2
	No	34	55
	Not Applicable	27	43
Protein C deficiency	Yes	6	10
	No	46	74
	Not Applicable	10	16
Protein S deficiency	Yes	9	15
	No	43	69
	Not Applicable	10	16
Antithrombin III deficiency	Yes	7	11
	No	44	71
	Not Applicable	11	18
Lupus anticoagulant	Yes	6	10
	No	53	85
	Not Applicable	3	5
Antiphospholipid antibodies	Yes	0	0
	No	57	92
	Not Applicable	5	8

Table 2: Relevant medical conditions and prescribed medications

Variable	Category	Sample (N=62)	Percentage (%)
Diabetes	Yes	18	29
	No	44	71
Chronic kidney disease	Yes	10	16
	No	52	84
Hypothyroidism	Yes	3	5
	No	59	95
Osteoporosis	Yes	3	5
	No	59	95
Malignancy	Yes	3	5
	No	59	95
Rheumatoid arthritis	Yes	6	10
	No	56	90
Systemic lupus erythematosus	Yes	4	6
	No	58	94
Psoriasis	Yes	1	2
	No	61	98
Pernicious anemia	Yes	0	0
	No	62	100
Folic acid	Yes	23	37
	No	39	63
Vitamin B6	Yes	15	24
	No	47	76
Vitamin B12	Yes	13	21
	No	49	79
Cyclosporine	Yes	1	2
	No	61	98
Fenofibrate	Yes	5	8
	No	57	92
Metformin	Yes	9	15
	No	53	85
Methotrexate	Yes	5	8
	No	57	92
Phenytoin	Yes	4	6
	No	58	94

Table 3: Confidence Intervals of Spearman's rho

	Spearman's rho	Significance (2-tailed)
Age - Homocysteine level	0.004	0.978
Age - Serum creatinine	0.16	0.213
Homocysteine level - Serum creatinine	-0.065	0.615

Table 4: Wilcoxon Rank Sum Test for relevant medical conditions

	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig (2-tailed)
Diabetes	330.5	1320.5	-1.02	0.308
Chronic kidney disease	185.5	1563.5	-1.431	0.152
Hypothyroidism	60.5	1830.5	-0.922	0.356
Osteoporosis	44.5	1755.5	-2.057	0.04
Malignancy	107	117	-0.259	0.796
Rheumatoid arthritis	80	1676	-2.103	0.035
Systemic lupus erythematosus	81	91	-1.007	0.314

Table 5: Wilcoxon Rank Sum Test for relevant prescribed medications

	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig (2-tailed)
Folic acid	364.5	1144.5	-1.229	0.219
Vitamin B6	244.5	1372.5	-1.782	0.075
Vitamin B12	274.5	1499.5	-0.764	0.445
Cyclosporin	30.5	1921.5	0	1
Fenofibrate	81.5	1735.5	-1.583	0.113
Metformin	211	256	-0.0552	0.581
Methotrexate	75	1728	-1.752	0.08
Phenytoin	97.5	107.5	-0.532	0.595

Table 6: Kruskal-Wallis H Test

	Kruskal-Wallis H	Df	Asymp Sig.
Factor V Leiden mutation	0.039	2	0.981
Protein C deficiency	1.612	2	0.447
Protein S deficiency	1.682	2	0.431
Antithrombin III deficiency	0.821	2	0.663
Lupus anticoagulant	3.282	2	0.194
Antiphospholipid antibodies	0.074	1	0.785
Ethnicity	2.311	3	0.51
Smoking	6.846	3	0.077