

Case report

Thromboembolic events and metabolic Hyperhomocysteinemia: Unraveling the links and clinical implications

ABSTRACT

Thromboembolic events, represents one of the major causes of morbidity and mortality worldwide. While traditional risk factors, are well-established, metabolic hyperhomocysteinemia has emerged as a novel and potentially modifiable risk factor. Elevated levels of homocysteine, have been implicated in the pathogenesis of thromboembolic events, highlighting the importance of recognizing hyperhomocysteinemia in clinical practice.

This article explores the relationship between thromboembolic events and Hyperhomocysteinemia by first reporting a case of a 20 years old man admitted to the CHU of Casablanca for a pulmonary embolism and in whom an hyperhomocysteinemia was diagnosed , then we will be highlighting the pathophysiology, clinical implications, and management strategies.

Keywords: Hyperhomocysteinemia, thromboembolic events, pulmonary embolism.

1. INTRODUCTION

Thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), represent significant medical emergencies due to their potential to cause morbidity and mortality. While many factors contribute to the risk of thromboembolism, hyperhomocysteinemia has emerged as a noteworthy but often underappreciated risk factor[23,24].

In the absence of a provoked thromboembolic episode, current etiological research is based on two axes according to age: thrombophilia before the age of 50 and occult neoplasia after age 50.

It should be noted that a blood count , blood calcium levels and a minimum chest X-ray should be performed for any first episode of unprovoked VTE, regardless of age. At present, thrombophilia assessment should be carried out ideally between the third and sixth month

after the diagnosis of thrombosis, and consists of: a complete blood count, a haemostasis work-up (PT, APTT, fibrinogen), an assay of fibrinolytic proteins (anti-thrombin-III, protein C and protein S) protein S; mutations in factor V Leiden and in the G20210A gene of the prothrombin gene; and a search for antiphospholipid syndrome and circulating anticoagulant.

Homocysteine is an amino acid derived from the catabolism of methionine. In several controversial studies, hyperhomocysteinemia (HHcy) is considered a thromboembolic risk factor when its level is higher than 15 M [1,2], Plasma homocysteine measurement has no formal indication [3,4].

The etiologies of acquired hyperhomocysteinemia are renal failure, hypothyroidism, neoplasia, consumption of toxic substances, iatrogenic and vitamin B6, B9 and B12 deficiencies [4].

This article describes the observation of a 20 year old patient with a thromboembolic event associated with metabolic hyperhomocysteinemia. It was compared with data in the literature.

2. PRESENTATION OF CASE

Our patient is a 20-year-old male, no previous history, non-smoker, athletic. He presented with sudden onset of right basithoracic pain and dyspnea.

Clinically, he is afebrile at 36.7° C, blood pressure 122/86 mmHg, symmetrical, heart rate 120 beats per minute (bpm), room air SpO2 97%.

Biological tests revealed HB at 13.9 g/dL (N = 13-18 g/dL) with mean corpuscular volume (MCV) at 100 fL (N = 80-100 fL). Hemostasis was unremarkable, with platelets at 296 G/L (N = 150-400 G/L), PT 100%, rTCA 1.03 (N = 0.8-1.2) and fibrinogen 4.33 g/L (N = 2-4 g/L). There was no biological inflammatory syndrome, no hydroelectrolytic disorders, corrected calcemia at 2.31 mM (N = 2.2-2.6 mM), normal renal and hepatic function.

Electrocardiogram showed sinus tachycardia incomplete right bundle-branch block. Arterial gasometry was unremarkable. D-dimer levels rose to 3300 ng/mL (N < 500 ng/mL). Thoraco-abdomino-pelvic angioscanner showed bilateral proximal PE. (**fig.1**)

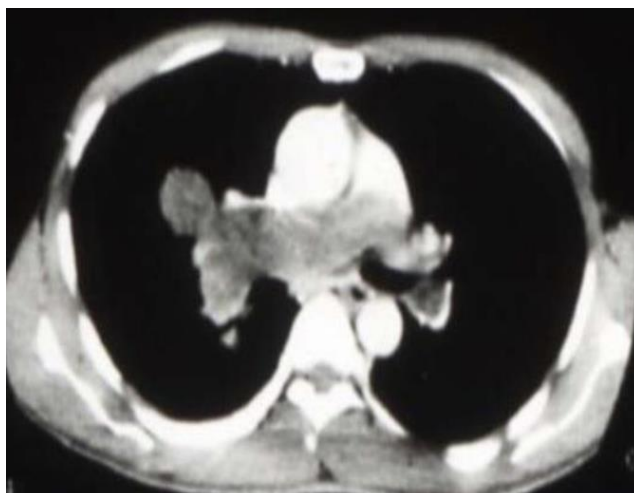


Fig. 1: chest angioscan of the patient showing bilateral proximal PE

Echocardiography revealed a massive thrombus in the right atrium (**fig.2**).

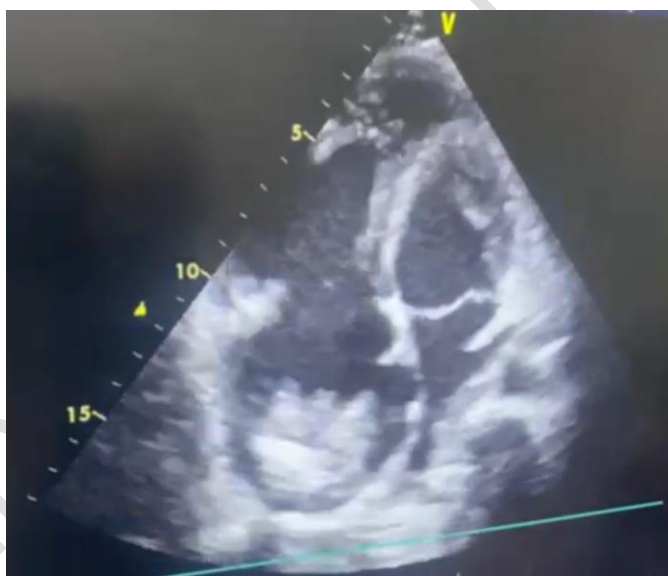


Fig. 2: Echocardiography of the patient revealing a massive thrombus in the right atrium

The patient had no change in general condition, palpable superficial adenopathy, splenomegaly or neurological signs. TSH was normal at 1.8 mIU/L (N = 0.5-5 mIU/L). Serum protein electrophoresis was normal. 24-hour proteinuria was negative. Viral serologies were negative, a Behcet's disease was initially suspected, but no Behcet criteria were found and the vasculitis work-up came back negative, as did an autoimmune work-up.

Prior to anticoagulation, thrombophilia testing revealed antithrombin-III at 93% (N = 70-130%), protein C at 77% (N = 70-130%), protein S at 92% (N = 70-130%), borderline ACC at 1.26 (N

< 1.20), rechecked negative, and no evidence of SAPL. Tests for mutations in the factor V Leiden and G20210A prothrombin genes were negative. Homocysteinemia, routinely performed in the emergency department, rose to 123.5 M (N < 10 M), vitamin assays showed normal vitamin B12 levels, but reduced folic acid levels.

The patient was supplemented with folates at a dose of 1000 g per day with periodic monitoring of homocysteine levels. With regard to anticoagulation, the initial low-molecular-weight heparin (LMWH) was replaced by rivaroxaban. The doses used were 15 mg twice a day for a total initial treatment period (including LMWH) of 21 days, then 20 mg a day for six months. Three months after stopping anticoagulation, the patient did not relapse.

3. DISCUSSION

A review of case reports in the literature was carried out, using the PubMed, Cochrane Library, and ScienceDirect article banks. The keywords used were, “venous thrombosis AND hyperhomocysteinemia”. Synonyms such as “pulmonary embolism” and “phlebitis” were also used in each search.

Hyperhomocysteinemia is a medical condition characterized by elevated levels of homocysteine in the blood.

Homocysteine is a nonprotein sulfhydryl amino acid derived from the metabolic conversion of methionine, this amino acid can be found in three forms: 70% is protein-bound, 30% is oxidized to the disulfides HcyHcy (homocysteine) and Hcy-cysteine (mixed disulfide), but only 1% is present as free Hcy [5].

Free and proteinbound Hcy and its disulfides are referred to globally as total Hcy (tHcy). The intracellular metabolism of Hcy happens through two pathways of remethylation to methionine and one pathway of trans-sulfuration to cysteine. The cofactor in the remethylation pathway is cobalamin, and the methyl group is donated by 5-methyl-tetrahydrofolate, the major form of folate, which derives from the reduction of 5,10-methylene-tetrahydrofolate by methylene-tetrahydrofolate reductase. There are many other vitamins in addition to cobalamin and folate that play a very crucial role in this pathway [5,6].

Niacin is mandatory for the formation of tetrahydrofolate; vitamin B2 is required to reduce 5,10-methylene-tetrahydrofolate to 5-methyltetrahydrofolate, which is the donor of methyl groups to Hcy to regenerate methionine. It is also needed to keep methionine synthase in a reduced-active state. Vitamin B6 is necessary to attach a carbon unit coming from the amino acid serine to tetrahydrofolate to make 5,10-methylene-tetrahydrofolate. In the other remethylation pathway, betaine is the methyl donor and the reaction is catalyzed by betainehomocysteine methyltransferase [7].

In the trans-sulfuration pathway, Hcy is transformed by cystathionine-b-synthase in cystathionine, with pyridoxal-50 -phosphate, a vitamin B6 derivative, acting as a cofactor. Vitamin B6 is also important for the transformation of cystathionine to cysteine and a-ketobutyric acid by cystathionase. Cysteine is a precursor of the important antioxidant

glutathione. Oxidation of the sulfur atom and further breakdown of cysteine happen through several enzymatic reactions [7]. (Fig.3).

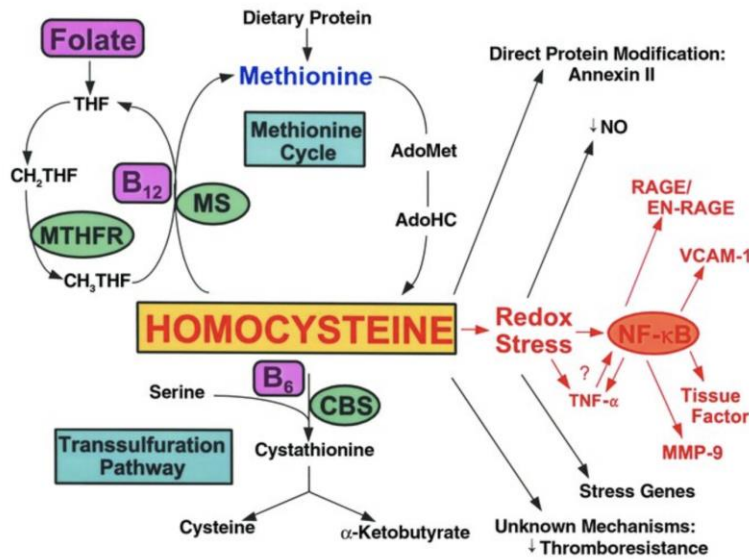


Fig. 3: homocysteine metabolism [8].

There is a noticeable increase of homocysteine with age and after menopause, and a decrease in fertile woman than in men. Renal dysfunction, caffeine and theine consumption, inadequate intake of vitamins B2, B6, B12 and folates, and genetic abnormalities are among the main determinants of homocysteine levels in the blood [9].

some drugs may interfere with the level of vitamin B12 like nitrous oxide, with folate like trimethoprim and with vitamin B6 like theophylline, this may be the cause of moderate hyperhomocysteinemia. we should also note an increase of homocysteinemia after a therapy with fibrates that is related to a functional reduction in renal function [10].

Some research also suggests that Sirtuin 1 may be involved in the regulation of homocysteine levels. This class-III NAD⁺-dependent deacetylases has been studied for its potential role in modulating thromboembolic risk factors [11]. In some research Sirtuin1 may have protective effects on endothelial function and vascular health, which could potentially mitigate the thromboembolic risk associated with hyperhomocysteinemia [12]. However, the specific mechanisms underlying the interaction between Sirtuin1 and thromboembolic risk in the context of hyperhomocysteinemia are still being elucidated.

to measure plasma tHcy, oxidized forms should be reduced to homocysteine, which can then be measured either directly or after derivatization. Many methods are currently available, including chromatographic methods (gas chromatography-mass spectroscopy and high-performance liquid chromatography) and manual or automated enzyme-linked immunosorbent assays. An international plasma standardization and analytical imprecision improvement are acquired to coordinate tHcy measurement. [13,14].

Research indicates a strong association between hyperhomocysteinemia and an increased risk of thromboembolic events. For patients who were not treated, the incidence of venous thromboembolism was as high as 10% per year [15]. An association with major and minor surgical procedures was noted in most of the episodes of the thrombo-embolic incidents.

Ridker et al, in a case-control study of 22,071 male physicians participating in the Physician Health Study, found an association between plasma tHcy levels and the risk of developing future episodes of idiopathic thromboembolic events over a 10-year period. Nevertheless, this association (idiopathic and secondary) was weaker and not statistically significant, as there was no association between high homocysteinemia and secondary VTE.[16] Another prospective study published in abstract form supported this observation, finding no association between hyperhomocysteinemia and the risk of postoperative deep vein thrombosis in patients undergoing elective hip arthroplasty and screened for postoperative DVT using bilateral phlebography [17].

Overall, elevated homocysteine levels are thought to contribute to thrombogenesis through several mechanisms:

- Endothelial Dysfunction: High homocysteine levels can damage the endothelium, the inner lining of blood vessels, reducing its ability to produce anticoagulant and vasodilatory substances like nitric oxide.
- Procoagulant State: Hyperhomocysteinemia promotes a procoagulant state by increasing the expression of clotting factors and reducing the activity of anticoagulant proteins such as thrombomodulin.
- Oxidative Stress: Elevated homocysteine levels generate reactive oxygen species (ROS), leading to oxidative stress, which further damages endothelial cells and promotes atherosclerosis and thrombosis.
- Platelet Activation: Hyperhomocysteinemia enhances platelet aggregation and adhesion, crucial steps in clot formation.

In 1998, Durand et al. described a probable alteration in thromboresistance: on the one hand, platelet activation and endothelial modification responsible for activation of the extrinsic pathway, and on the other, indirect inhibition of binding of the fibrinolytic protein C-tissue plasminogen activator (tPa) system.

The Ospina-Romero et al. cohort showed no association between HHcy and increased thromboembolic risk when smoking status and BMI were taken into account [2].

According to Sanchez et al., the indications for thrombophilia testing are: first unprovoked thromboembolic episode before age 50 in patients with a 1st-degree family history, recurrent VTE including at least one episode before age 50, venous thrombosis at an atypical site (cerebral, splanchnic, upper limb). Thrombophilia testing is no longer routinely recommended after a first unprovoked thromboembolic episode.

Management of hyperhomocysteinemia involves both addressing the elevated homocysteine levels and mitigating the risk of thromboembolic events. Key strategies include:

Nutritional Supplementation: Studies have shown that daily intake of folic acid, vitamin B6, and vitamin B12 can significantly reduce homocysteine concentrations, but In 2007, Heijer

and al. reported that this vitamin treatment did not reduce the risk of thromboembolic recurrence [18]. However, severe elevation in homocysteine level should be corrected with appropriate vitamin therapy to prevent vascular complications [19].

An international survey, which included 158 patients who were observed for a mean of 17.9 years, showed that treatment with high-dose vitamins reduced the plasma tHcy levels below 20 mM in only about half of the patients [20]. But the treatment was associated with a dramatic decrease in the incidence of vascular events. Dietary activators of Sirtuin 1 may also be considered along with a low salt diet. A recent publication reports that dietary supplementation of omega-3 fatty acids is effective in reversing the reduction of sirt1 levels in rats [21].

A study by Qureshi et al. raises the place of citicoline as a treatment to reduce HHcy [22], but it has no marketing authorization (MA).

Encouraging patients to adopt a healthy Mediterranean diet, alongside regular physical activity, can also support overall cardiovascular health and reduce thromboembolic risk.

Anticoagulation Therapy such as warfarin or direct oral anticoagulants (DOACs) are essential to prevent further clot formation. Monitoring and adjusting treatment based on individual risk factors, including hyperhomocysteinemia, is crucial.

Not to forget the periodic monitoring of homocysteine levels in patients with known hyperhomocysteinemia which helps to ensure that levels remain within a safe range and allows for timely adjustments in treatment.

4. CONCLUSION

Thromboembolic events associated with metabolic hyperhomocysteinemia represent a complex and multifactorial condition that requires a comprehensive approach.

In our patient's case, it is likely that hyperhomocysteinemia was responsible for his thromboembolic event, especially as the entire etiological work-up was carried out and came back negative. An unknown "decompensating" factor may also be present, potentiating a latent thrombogenic risk. Sirtuin 1 inhibitors could also be researched in our patient and reduced to prevent further thrombosis incident.

Continued research efforts are needed to further elucidate the role of hyperhomocysteinemia in thrombosis and develop personalized therapeutic strategies to mitigate thrombotic risk in affected individuals.

CONSENT

As per international standards or university standards, patient written consent has been collected and preserved by the author.

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

REFERENCES

1. Durand P, Prost M, Blache D. Altérations du métabolisme de l'homocystéine et maladies cardiovasculaires. *Rev Fr Laboratoires* 1998;307:33–44. French
2. Ospina-Romero M, Cannegieter SC, den Heijer M, Doggen CJM, Rosendaal FR, Lijfering WM. Hyperhomocysteinemia and risk of first venous thrombosis: the influence of (unmeasured) confounding factors. *Am J Epidemiol* 2018;187(7):1392–400.
3. Roux A, Sanchez O, Meyer G. Quel bilan de thrombophilie chez un patient atteint de maladie veineuse thromboembolique ? *Reanimation* 2008;17(4):355–62. French
4. Veyrat-Durebex C, Blasco H, Crinier J, Vayne C, Emond P, Labarthe F, et al. Investigation of hyperhomocysteinemia. *Ann Biol Clin* 2013;71(5):517–25
5. Refsum H, Smith AD, Ueland PM, et al. Facts and recommendations about total homocysteine determinations: an expert opinion. *Clin Chem* 2004;50:3–32
6. Finkelstein JD. Methionine metabolism in mammals. *J Nutr Biochem* 1990;1:228–257
7. Cattaneo M. (2006). Hyperhomocysteinemia and Venous Thromboembolism. *Seminars in Thrombosis and Hemostasis*, 32(7), 716–723.
8. *J Clin Invest*. 2001;107(6):663-664. <https://doi.org/10.1172/JCI12369>.
9. Jacques PF, Bostom AG, Wilson PW, Rich S, Rosenberg IH, Selhub J. Determinants of plasma total homocysteine
10. Cattaneo M. Hyperhomocysteinemia, atherosclerosis and thrombosis. *Thromb Haemost* 1999;81:165–176
11. Kane, A.E.; Sinclair, D.A. Sirtuins and NAD⁺ in the development and treatment of metabolic and cardiovascular diseases. *Circ. Res.* 2018, 123, 868–885.
12. Ching-Hou Ma, Yen Chun Chiu, Chin-Hsien Wu, I.-Ming Jou, Yuan-Kun Tu, Ching-Hsia Hung, Pei-Ling Hsieh, Kun-Ling Tsai. Homocysteine causes dysfunction of chondrocytes and oxidative stress through repression of SIRT1/AMPK pathway: A possible link between hyperhomocysteinemia and osteoarthritis, *Redox Biology*, Volume 15, 2018, Pages 504-512,
13. Tripodi A, Chantarangkul V, Lombardi R, Lecchi A, Mannucci PM, Cattaneo M. Multicenter study of homocysteine measurement. Performance characteristics of different methods, influence of standards on interlaboratory agreement of results. *Thromb Haemost* 2001;85:291–295
14. Hanson NQ, Eckfeldt JH, Schwinchtenberg K, Aras O^o, Tsai MY. Interlaboratory variation of plasma total homocysteine measurements: results of three successive homocysteine proficiency testing surveys. *Clin Chem* 2002;48:1539–1545
15. Mudd SH, Levy HL, Skovby F. Disorders of transsulfuration. In: Scriver CR, Beaudet AL, Sly WS, et al eds. *The Metabolic and Molecular Bases of Inherited Disease*. New York: McGraw-Hill; 1995:1279–1327
16. Ridker PM, Hennekens CH, Selhub J, Miletich JP, Malinow MR, Stampfer MJ. Interrelation of hyperhomocyst(e)inemia, factor V Leiden, and risk of future venous thromboembolism. *Circulation* 1997;95:1777–1782
17. Cattaneo M, Zighetti ML, Turner RM et al and the ECAT DVT Study Group. Fasting plasma homocysteine levels do not predict the occurrence of deep-vein thrombosis after elective hip replacement surgery. *Neth J Med* 1998;52(suppl): S21
18. den Heijer M, Willems HPJ, Blom HJ, Gerrits WBJ, Cattaneo M, Eichinger S, et al. Homocysteine lowering by B vitamins and the secondary prevention of deep vein

- thrombosis and pulmonary embolism: a randomised, placebo-controlled, double-blind trial. *Blood* 2007;109(1):139–44.
19. Melhem A, Desai A, Hofmann MA. Acute myocardial infarction and pulmonary embolism in a young man with pernicious anemia-induced severe hyperhomocysteinemia. *Thromb J.* 2009;7:5.
 20. Yap S, Boers GH, Wilcken B, et al. Vascular outcome in patients with homocystinuria due to cystathionine betasynthase deficiency treated chronically: a multicenter observational study. *Arterioscler Thromb Vasc Biol* 2001;21:2080– 2085
 21. Wu A, Ying Z, Gomez-Pinilla F. Omega-3 fatty acids supplementation restores mechanisms that maintain brain homeostasis in traumatic brain injury. *J Neurotrauma.* 2007;24:1587–1595.
 22. Qureshi SS, Gupta JK, Goyal A, Narayan Yadav H. A novel approach in the management of hyperhomocysteinemia. *Med Hypotheses* 2019;129:109245.
 23. Cattaneo M. Hyperhomocysteinemia and thrombosis. *Lipids.* 2001 Jan;36(S1):S13-26.
 24. Cattaneo M. Hyperhomocysteinemia: a risk factor for arterial and venous thrombotic disease. *International Journal of Clinical and Laboratory Research.* 1997 Dec;27:139-44.

ABBREVIATIONS

DVT : deep vein thrombosis
LMWH : low-molecular-weight heparin
PE : pulmonary embolism