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Hyperhomocysteinemia – A Death Warrant in Young

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ABSTRACT

Patient with atherosclerotic narrowing of blood vessels develop thrombotic occlusion and present clinically with cerebrovascular accidents, coronary artery disease, chronic kidney disease and peripheral vascular disease, with the main risk factors for atherosclerosis being diabetes mellitus, dyslipidemia, systemic hypertension, advanced age, male sex, obesity and smoking. But there are many other causes of arterial occlusion in the young, such as nonatherosclerotic angiopathies, thrombophilias, genetic disorders, inflammatory and infectious vasculitis. This is a case where thrombotic occlusion has occurred in the coronary and cerebral circulation in a young patient due to thrombophilia.

Keywords: Hyperhomocysteinemia, arterial and venous thrombosis, coronary artery disease and stroke in young patients, vitamin B12, folic acid

Hypercoagulability of the blood occurs in various diseases causing vascular occlusion. Compared to thrombotic occlusion due to atherosclerosis, it occurs in younger age group, it can be venous or arterial, can be recurrent and can occur in blood vessels which are not usually involved in atherosclerosis. Here is one such case.

CASE REPORT

A 21-year-old male was admitted with generalized tonic-clonic seizures. The patient gave 4 months history of coronary artery disease (CAD) - acute anterior wall myocardial infarction (AWMI) with left ventricular (LV) dysfunction and echocardiography showed LV clot. The patient was started on aspirin 75 mg, warfarin 2 mg, enalapril 5 mg, metoprolol 25 mg and diuretics. Due to the LV clot, the patient developed an embolic stroke about 2 months later with a neurological deficit as left-sided hemiparesis. Following treatment, hemiparesis improved and the patient was able to walk without support. The patient was treated for the seizures and there was no recurrence.

The following investigations were done:

- Hemoglobin - 11.8 g/dL
- White blood cell (WBC) - 7,000/mm^3
- Platelets - 1,83,000/mm^3
- Serum creatinine - 0.8 mg/dL
- Blood urea - 28 mg/dL
- Serum glutamic-pyruvic transaminase (SGPT) - 18 U/L
- Prothrombin time (PT) - 22.6 seconds
- Activated partial thromboplastin time (aPTT) - 46 seconds
- PT: International normalized ratio (INR) - 2.05
- Serum cholesterol - 143 mg/dL
- Serum triglycerides - 176 mg/dL
- Serum homocysteine - 18.53 μmol/L (1-15.39)
- Antiphospholipid IgG - 1.3 GPL U/mL (0-10)
- Antiphospholipid IgM - 1.6 GPL U/mL (0-10)
- 2D Echocardiography – CAD - AWMI with severe LV dysfunction, EF - 35%, LV apical thrombus, akinetic septum and lateral wall
- Coronary angiogram – Proximal left anterior descending artery - 50% lesion with Grade 2

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thrombus and Thrombolysis In Myocardial Infarction (TIMI) Grade 2 flow distally.

The patient was again readmitted with history of fever, vomiting, abdominal pain and loose stools. The patient was clinically stable but on the third day after admission, his condition deteriorated. He was shifted to intensive care unit (ICU). The patient became dyspneic with a drop in oxygen saturation and blood pressure. He was further managed with invasive ventilation and inotropic support with noradrenaline and dopamine. Echocardiography showed an ejection fraction (EF) of 20% with moderate mitral regurgitation and generalized LV hypokinesia. Despite treatment, the patient did not improve and died of cardiac failure. Previous investigations had already revealed hyperhomocysteinemia in plasma. Treatment was given with both vitamin B12 and folic acid.

Table 1. Causes for Nonatherogenic Occlusion of Blood Vessels

Nonatherosclerotic angiopathies	Cervicocephalic arterial dissection
	Cerebral amyloid angiopathy
	Moyamoya disease
	Fibromuscular dysplasia
	Reversible cerebral vasoconstriction syndrome
	Susac's syndrome
	Sneddon's syndrome
	Migraine-induced stroke
Hematologic conditions	Hypercoagulable state due to deficiencies of protein S, protein C or antithrombin; factor V Leiden mutation, prothrombin gene G20210A mutation
	Acquired hypercoagulable state (e.g., cancer, pregnancy, hormonal contraceptive use, exposure to hormonal treatments such as anabolic steroids and erythropoietin, nephrotic syndrome)
	Antiphospholipid syndrome
	Hyperhomocysteinemia
	Sickle cell disease
	Myeloproliferative disorders (e.g., leukemia, lymphoma)
Genetic	Fabry disease
	CADASIL
	MELAS
	Marfan syndrome
	Neurofibromatosis
	Sturge-Weber disease
Inflammatory and infectious	Vasculitis (primary angiitis of the CNS, Sjogren's syndrome, Wegener's granulomatosis)
	Temporal arteritis
	Takayasu disease
	Behcet's syndrome
	Neurosarcoidosis
	Neurocysticercosis
	HIV
	Varicella zoster virus
	Neurosyphilis
	Tuberculous meningitis

CADASIL = Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MELAS = Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episode; CNS = Central nervous system; HIV = Human immunodeficiency virus.

This young patient was admitted four times within a span of 5 months and had both cerebrovascular accident (CVA) and acute myocardial infarction and had occlusion of both cerebral and coronary arteries leading to death despite treatment for hyperhomocysteinemia, which is vitamin B12 and folic acid replacement.

DISCUSSION

There are many causes for nonatherogenic occlusion of blood vessels leading to CVA, CAD and other vaso-occlusive diseases in young individuals. Table 1 shows the major causes of such events.

Thrombophilia is an inherited or acquired tendency to develop thrombosis. Thrombophilia can cause thrombosis by manufacturing too much clotting proteins, making abnormal clotting proteins that are resistant to breakdown, producing too little of proteins that prevent thrombosis or damaging the walls of blood vessels.

This patient is a case of thrombophilia due to hyperhomocysteinemia. Elevated levels of homocysteine produce arterial and venous thrombosis as well as the development of atherosclerosis. In the other causes of thrombophilia, the pathology is more of hypercoagulability of blood causing thrombosis and atherosclerosis does not play a major part.

The prothrombotic effects of homocysteine are due to thioester linkages formed between homocysteine metabolites and many proteins, including fibrinogen. Marked elevation of homocysteine may be caused by an inherited deficiency of cystathionine beta-synthase. Much more common is a variant form of 5,10-methylenetetrahydrofolate reductase which causes mild homocysteinemia in 5-15% Caucasians and eastern Asians. It is characterized by increased concentration of sulfur-containing amino acid homocysteine in the blood and urine. Many patients present in childhood. Life-threatening vascular complications of coronary, renal and cerebral arteries can occur. Some patients develop a marfanoid habitus and radiological evidence of osteoporosis. Hyperhomocysteinemia has 9 distinct clinical disorders. The classic disease shows evidence of elevated free homocysteine in plasma. Homocysteine acts not only as a thrombophilic agent but also as an atherogenic agent. Vascular occlusions can occur in the arteries and veins.

Treatment involves giving folate and vitamin B12 supplements. They reduce the homocysteine levels but have limited effects on cardiovascular disease.

CONCLUSION

Homocysteinemia often goes undiagnosed as a cause of CAD and stroke. It has to be ruled out in all young patients with arterial and venous thrombosis. But the sad state of affairs is such that although treatment is with only vitamin B12 and folic acid replacement, which is freely available, patients often succumb to the disease.

SUGGESTED READING

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Common Causes of Pediatric Allergic Contact Dermatitis

The leading three contact allergens in patients below 18 years of age include hydroperoxides of linalool, nickel sulfate and methylisothiazolinone, suggests an analysis of data from the Pediatric Allergic Contact Dermatitis Registry.

This registry is the first multicenter prospective database in the United States focusing on pediatric allergic contact dermatitis. Investigators obtained data on 218 patients below 18 who were referred for an evaluation of allergic contact dermatitis at one of the 10 participating sites from January 2016 through June 2020. The mean number of allergens patch tested per child was 78. Nearly 81% of the children had one or more positive patch test reactions, with the rate being more or less similar among those with and without a history of AD (80% vs. 82%, respectively). The five top allergens were hydroperoxides of linalool (22%), nickel sulfate (19%), methylisothiazolinone (17%), cobalt chloride (13%) and fragrance mix I (12%). The findings were presented at the virtual annual meeting of the Society for Pediatric Dermatology… (*Medscape*)