

The tricky thrombus: A rare inborn error of metabolism with venous thrombosis

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Abstract

Hyperhomocysteinemia is an inborn error of amino acid metabolism (IEM) in which homocysteine accumulates in the blood and produces a slowly evolving clinical syndrome.⁽¹⁾ Late presentation is rarely seen in paediatric age group.⁽²⁾ An eight year old male child presented with diffuse left lower limb swelling (below knee upto medial malleolus) with complete longitudinal and transverse thrombosis of popliteal vein and posterior tibial vein this was later diagnosed with Hyperhomocysteinemia.

Keywords: Homocystinuria, Homocysteinemia, Hyperhomocysteinemia.

Introduction

Hyperhomocysteinemia is an inherited multisystemic metabolic disorder, associated with the deficiency of the enzyme cystathionine-beta-synthase which causes defect in the transsulfuration pathway (homocystinuria I) or methylation pathway (homocystinuria II and III); leading to excessive accumulation of homocysteine.⁽³⁾ The prevalence of Hyperhomocysteinemia is about 1:200,000–300,000 in general population of United States.⁽⁴⁾

It is associated with a higher incidence (0.05 per 1,000 per year) of thromboembolic complications (stroke, vascular injury) and high mortality.^(5,6,7,8) Thromboembolism may lead to serious complications like optic atrophy (secondary to occlusion of optic artery); hemiparesis; severe hypertension (because of renal infarcts); seizures or focal neurological signs (due to cerebral thrombi).⁽⁹⁾

Brattstrom L E et al, found role of folic acid administration in normal individuals who were not folate deficient, in reducing the plasma homocysteine level.⁽¹⁰⁾ Betaine is a methyl group donor involved in the metabolism of methionine and has been suggested as a possible treatment for Hyperhomocysteinemia.⁽¹¹⁾ This is a case of Hyperhomocysteinemia with venous involvement leads to abscess formation without ectopia lentis which gained complete venous recanalisation.

Case Report

An eight year old boy, born of non-consanguineous marriage, second at birth order, presented with seven days history of intermittent fever with pain and swelling of left lower limb below the knee. It started as puffiness around left medial malleolus which progressed gradually to involve whole leg below knee till day-7 of illness. Child had no history of trauma, insect bite, animal bite, prolonged immobilization, hypertension, ulcer, gangrene, loss of sensation, recent hospitalization, major surgery and similar episodes in the family. Mother had history of one intrauterine death

(first in order) at eight month of gestation and neonatal death of one male child (third in order) at one hour of life due to extreme prematurity. Milestones achieved normally with corresponding age without scholastic or behavioural issues; currently studying in second standard with average performance. On examination at day-8 of illness (first day of admission to our hospital) child was conscious, oriented, afebrile with BP=106/66 mm of Hg (between 50th and 97th centiles). No marfanoid appearance and skeletal abnormalities like genu valgum, pes cavus, spine and chest abnormalities noted. No hepatosplenomegaly and other abdominal mass recorded.

At local examination, diffuse edema non pitting type at left lower leg with cellulitis extending from medial malleolus upto the knee was present. All central & peripheral pulses were well felt except for Dorsalis pedis of left foot. No inguinal lymph nodes were noted. Skin was shiny with calf tenderness. Colour-doppler showed complete thrombosis (complete longitudinal and transverse involvement) of popliteal vein and posterior tibial vein with normal doppler study of right lower limb. No arterial abnormal blood flow was noticed. Later, limb cellulitis transformed into abscess confirmed by ultrasonography. Haemogram showed total leucocyte counts of 32900, hemoglobin-10.8, hematocrit-32.9 and platelet counts-1.63 lac on day of admission. Total cholesterol was 148 mg/dl with triglycerides of 178 mg/dl; PT, aPTT, INR-normal range; haemoglobin electrophoresis- normal; Serum homocysteine – 32 µmol/L by enzymatic recycling (normal range <15 mmol/l) and homocysteine was found positive in urine (silver nitrate based).

Incision and Drainage was done for left leg abscess and pus culture had growth of Methicillin Sensitive Staphylococcus Aureus (MRSA) which was treated with 21 days of intravenous vancomycin (dose 60 mg/kg/day) as per sensitivity pattern. Child was started on low molecular weight Heparin (Enoxaparin) with dose of 2 mg/kg/day. Dietary modification (food rich in folic-acid, vitamin B12, B6) was done. For

Hyperhomocysteinemia, child was supplemented with Folic acid and Vitamin B6 without multivitamin. After stabilisation, Warfarin was started with regular monitoring of PT, INR. Repeat doppler showed complete recanalisation of the deep vein on day-14 of admission.

Discussion

This entity was first described by Nina A. J. Carson et al in 1963 in urine samples from intellectually deficient people in Northern Ireland followed by McCully in 1969, at autopsy, in a seven week old infant who died due to high level of homocysteine.^(12,13,14) Homocysteine promotes thrombosis by stimulation of thromboxane A₂; induction of endothelial cell tissue factor expression; activation of the procoagulant endothelial cell factor V and inactivation of the anticoagulant substances protein C and thrombomodulin; and blocking the tissue plasminogen activator binding domain of annexin II.^(15,16,17) Hyperhomocysteinemia is the second most common inborn error of amino acid metabolism after Phenylketonuria.⁽¹⁸⁾

The common presenting features are ectopia lentis (95%), intellectual disability (86%), dental anomalies (40%), osteoporosis (40%), behavioural problems (33%), arachnodactyly (13%) and vascular events such as deep vein thrombosis (DVT), sagittal sinus thrombosis and myocardial infarction.^(19,20)

According to the degree of homocysteine elevation, Hyperhomocysteinemia may be classified as: Mild: 15–30 $\mu\text{mol/L}$ (prevalence in population <10); Moderate: 30–100 $\mu\text{mol/L}$ (prevalence <1%) and Severe: above 100 $\mu\text{mol/L}$ (prevalence <0.02%).⁽⁴⁾ Association between mild Hyperhomocysteinemia and venous thrombosis has also been reported.⁽²¹⁾ Hyperhomocysteinemia is an established risk factor for venous thrombosis and vascular disease with systemic involvement of eyes, skeleton, vascular system and central nervous system.⁽²²⁾ Because of numerous complications, such as increased tendency to strokes, ocular symptoms and neuropsychiatric abnormalities, regular medical follow-up is imperative.⁽²³⁾ In the majority of untreated individuals, ectopia lentis occurs by the age of eight years but in this case no eye abnormality was present.^(24,25) Venous thromboembolism, including DVT and pulmonary embolism, accounts for at least 50% of the vascular events in Hyperhomocysteinemia which was put debateable by study of Tore Amundsen et al.^(26,27) Martin Den Heijer et al measured plasma homocysteine levels in 269 patients with a first, objectively diagnosed episode of DVT and found high plasma homocysteine levels as a strong risk factor for DVT.⁽²¹⁾ Effect of mild Hyperhomocysteinemia in thrombosis is less documented but this case manifested DVT even with mild increase in dose of homocysteine.⁽²⁸⁾ Recurrent thrombo-embolic events have also been reported in case

of severe Hyperhomocysteinemia.⁽²⁹⁾ A single plasma total homocysteine measurement usually reflects the mean homocysteine concentration and is adequate in most settings; but due to greater variability in populations, measurements from two blood samples collected 2–4 weeks apart will improve the quality of such studies.⁽³⁰⁾ Single sample was collected in this patient due to financial constraints. Thrombophilic disorder work-up (like Factor V Leiden, protein C, protein S, antithrombin III and fibrinogen levels) should be delayed till completion of anticoagulant therapy because it may be false-positive during acute episode of thrombosis that can act as acute phase reactant. Test should be done after 2 weeks of discontinuation of therapy but in this patient test not done because still on anticoagulant therapy.^(31,32,33)

Thrombolytic agents, when administered within 2 weeks of onset of symptoms, are most effective in restoring the venous patency.^(34,35) Child was started with anti-coagulant therapy as soon as complete obstruction of deep vein was detected which gave good outcome. Similar results were obtained by Chiung-Zuan Chiu et al.⁽³⁶⁾ Various associations suggest consideration of antithrombotic therapy in case of life/organ/limb-threatening thrombosis with balance of benefit to risk ratio.^(37,38) In a 10 years follow-up study of patients with Hyperhomocysteinemia favourable outcome was noted who diagnosed and treated earlier in the form of clinical responses for growth index, controlled refractory seizures, neurodevelopmental status and neuroimaging findings.⁽³⁹⁾

Conclusion

Hyperhomocysteinemia is a rare presentation in paediatric age group. Late presentation or silent form of this congenital disease is rarely reported. Child may present with purely venous manifestation with abscess and without ectopia-lentis.

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