2020 FAMILY MEDICINE MIDWEST CONFERENCE

Ischemic stroke seen in Homocystinuria

Monica Anil Lukose

THE FLEXIBILITY OF FAMILY MEDICINE IN A CHANGING WORLD
NOVEMBER 13 - 14, 2020

Speaker

Monica Anil Lukose

DISCLOSURE

Faculty Disclosure Statement
The Illinois Academy of Family Physicians adheres to the conflict of interest policy of the ACCME and the AMA. It is the policy of Illinois AFP to ensure balance, independence, objectivity, and scientific rigor in all its educational activities. All individuals in a position to control the content in our programs are expected to disclose any relationships they may have with commercial companies whose products or services may be mentioned so that participants may evaluate the objectivity of the presentations. In addition, any discussion of off-label, experimental, or investigational use of drugs or devices will be disclosed by the faculty. Only those participants who have no conflict of interest or who agree to an identified resolution process prior to their participation were involved in the CME activity.?

Ischemic stroke seen in Homocystinuria

TABLE OF CONTENTS

HISTORY

37 year old male with a history of homocystinuria (on thiamine, B12, and folate therapy) who presented to our emergency department with concerns of nausea and multiple episodes of non-bloody, non-bilious emesis, with accompanying headache and dizziness which began suddenly earlier that day.

DETAILS OF HISTORY

Patient denied any sick contacts, eating anything unusual

Patient was a non-smoker, denied any drugs or excessive alcohol use.

Patient's vitals are remarkable for sinus tachycardia (HR >150) on presentation, with no focal neurological deficits.

Rapid and PCR testing for COVID-19 were negative.

Well's Score 4.5.

ADDITIONAL HISTORY

Past Medical History

homocystinuria)

Past surgical History

None

Family history

None

Past Social History

non-smoker,
denied any
drugs or
excessive
alcohol use

Home medications

thiamine,
B12,
folate therapy

Allergies

None

REVIEW OF SYSTEMS

Constitutional: reports nausea and vomiting; denies fever or chills
HEENT: Denies eye pain and redness, headache, mouth ulcers
Cardiovascular: Denies chest pain or palpitations
Pulm: Denies shortness of breath
Gastrointestinal: Denies diarrhea or abdominal pain.
Genitourinary: Denies dysuria or hematuria
Musculoskeletal: Denies back pain or joint pain
Skin: Denies rash or jaundice
Neurological: Endorses weakness and right arm twisted but denies numbness, dizziness
Heme/Lymph: Reports anemia, denies bruising or lymphadenopathy
Psych: Denies history of depression or anxiety

PHYSICIAL EXAM

5’ 6”, 84 kg
VS: 98 F (oral), HR 94, BP 118/68, RR 15, O2 98% RA, orthostatics positive: 120/63 supine, 93/63 standing

Constitutional: No acute distress
HEENT: Mucus membranes dry, conjunctiva pale, no oral ulcers
Neck: Supple, no lymphadenopathy
Chest: Normal expansion, no chest wall tenderness
Respiratory: Clear to auscultation bilaterally, no wheezing or crackles
Cardiovascular: Regular rate and rhythm, normal S1 S2, no murmur/gallop/rub. Capillary refill normal, 2+ pulses
Abdomen: Hyperactive bowel sounds, mild diffuse tenderness, no hepatosplenomegaly, well-healed surgical scars, no hernia on coughing, no rebound tenderness
Rectal: Normal rectal exam except for positive hemoccult; no anal fissure, no hemorrhoids
Extremities: No edema, no calf tenderness, no joint tenderness
Neurological: Cranial nerves II-XII grossly intact, strength 5/5 in all extremities, reflexes 2+, sensory intact, gait normal, no tremor
Skin: no rash, erythema, ecchymotic patches, flushing, or hyperpigmentation
Mental Status: Alert and oriented to person, place, and time

DIFFERENTIAL DIAGNOSIS

- Stroke?
- Gastroenteritis?

INITIAL LABS

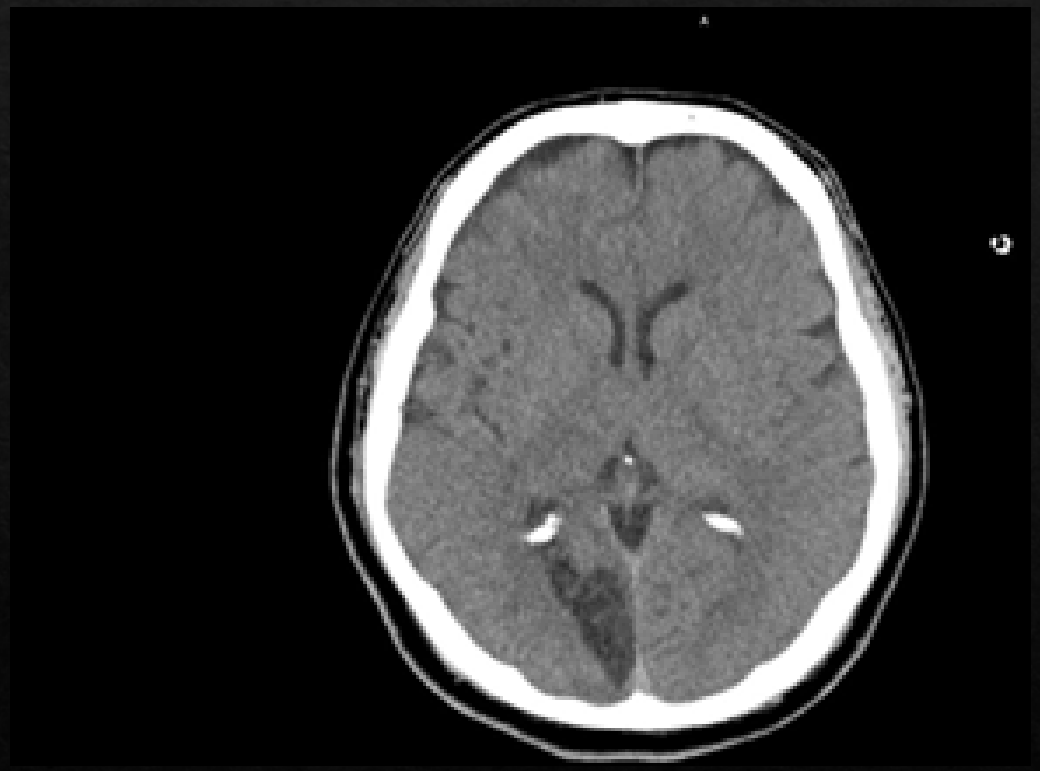
Test	Result	
COVID-19 (NAA)	NEGATIVE	Apr 21, 2020
SARS-CoV-2 Source	NP SWAB	Apr 22, 2020
SARS-CoV-2 (PCR)	Not Detected	Apr 22, 2020

ABG pH	7.17 *L	Apr 21, 2020
ABG pCO2	66.00 H	Apr 21, 2020
ABG pO2	108.00 H	Apr 21, 2020
ABG HCO3	24.10	Apr 21, 2020
ABG O2 Saturation	98.90	Apr 21, 2020

Urine Protein	30 H	Apr 21, 2020
Urine Ketones	TRACE H	Apr 21, 2020

Urine Bacteria	RARE A	Apr 21, 2020
Urine Glucose	50 H	Apr 21, 2020

INITIAL IMAGING



CT BRAIN

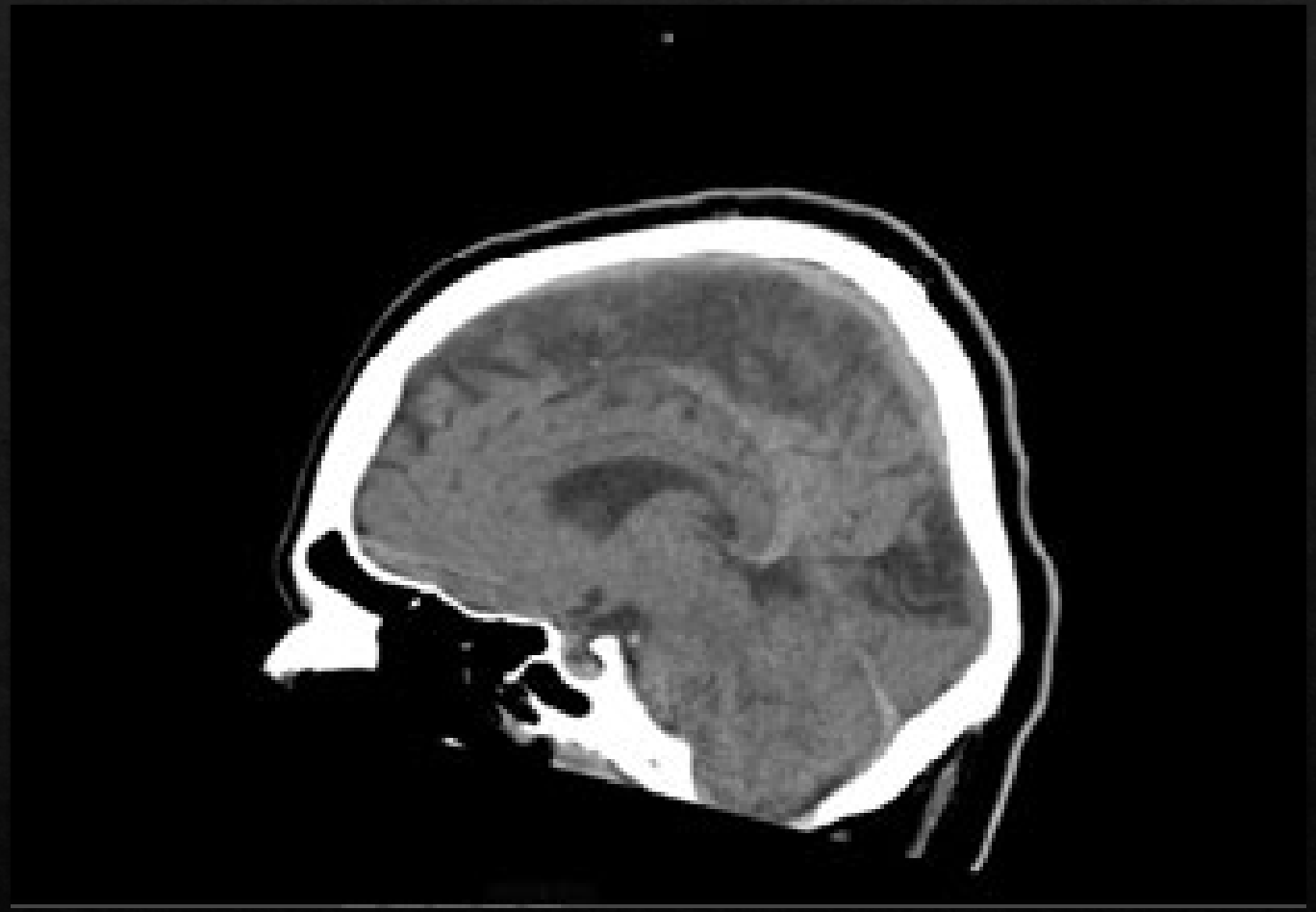
occipital encephalomalacia

TURN OF EVENTS

While awaiting studies in the ED, the patient suddenly became unresponsive and pulseless. ACLS was begun immediately, with return of spontaneous circulation after four rounds of epinephrine. Patient was intubated for airway protection and placed on full ventilator support. Hypothermia protocol was not initiated due to coagulopathy.

Once patient was able to undergo further imaging studies

- CTA of the head and neck showed multiple vertebral, posterior cerebral, and basilar arterial occlusions, in addition to a large right subclavian arterial thrombus at the takeoff of the vertebral artery – which may represent the source of embolism to the posterior circulation of the brain, and perhaps may have even represented the cause of the patient's cardiac arrest.
- CTA of the chest was negative for pulmonary embolism.
- Repeat CT brain imaging post-arrest showed signs indicative of early anoxic brain damage, with diminished brainstem reflexes on physical examination (no corneal reflexes, no gag, sluggish pupillary response off sedation).
- Patient was admitted to the medical intensive care unit (ICU) for post cardiac arrest / post ischemic cerebral vascular accident / and ventilator management.



HOSPITAL COURSE

- When the patient was admitted to the ICU, our general neurology service determined after reviewing the images that given the duration of symptoms (greater than 12 hours), findings on plain CT (encephalomalacia with now early signs of anoxic brain injury), and poor brainstem reflexes on physical examination, the patient was not a candidate for mechanical thrombectomy.

- Hematology recommended the patient therefore continue on anticoagulation via a heparin drip which was begun in the Emergency Department.

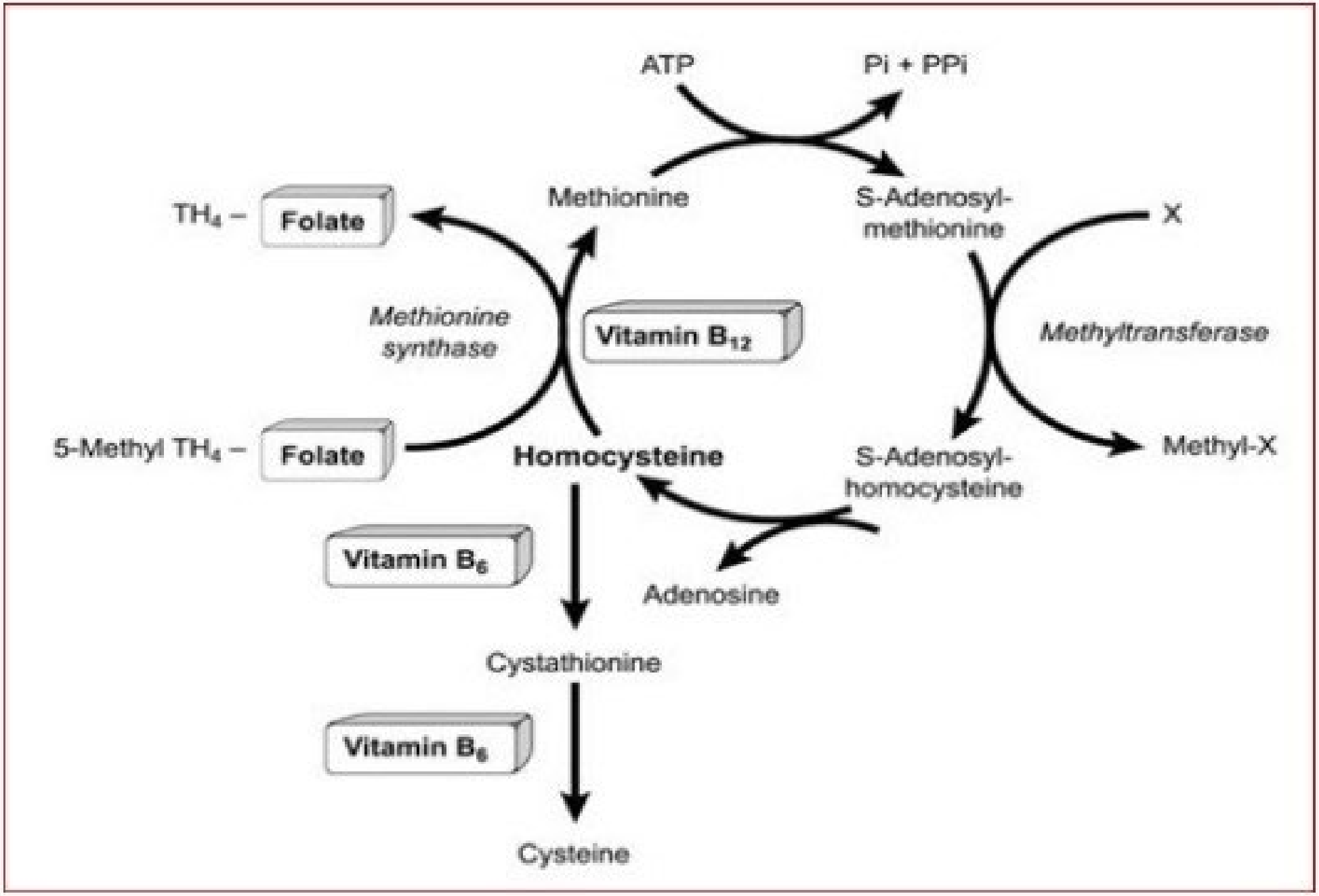
- Additionally, the patient was outside the window for tPA therapy.

- Prior to brain MRI imaging, the patient was accepted to a University Neurology Center for a higher level of care and was transferred out.

ISCHEMIC STROKE IN HOMOCYNTINURIA

INTRODUCTION

- Hyperhomocystinemia is a known risk factor for the development of intra-arterial thrombosis without apparent underlying atherosclerotic disease
- Elevated homocysteine in the blood is believed to damage connective tissue proteins such as collagen – leading to impairment of the integrity of the vascular walls and promoting the formation of clots.
- USPSTF have warned that those with homocysteine levels greater than 5 micromol/L have an associated 20% greater risk of developing vascular pathologies such has coronary artery disease, as well as increasing the risk of developing peripheral artery disease.


ATP
Pi + PPi
Methionine
S-Adenosyl-
methionine
X
TH_4 –
Folate
Methionine
synthase
Vitamin B_{12}
Methyltransferase
5-Methyl TH_4 –
Folate
Homocysteine
S-Adenosyl-
homocysteine
Methyl-X
Vitamin B_6
Adenosine
Cystathionine
Vitamin B_6
Cysteine

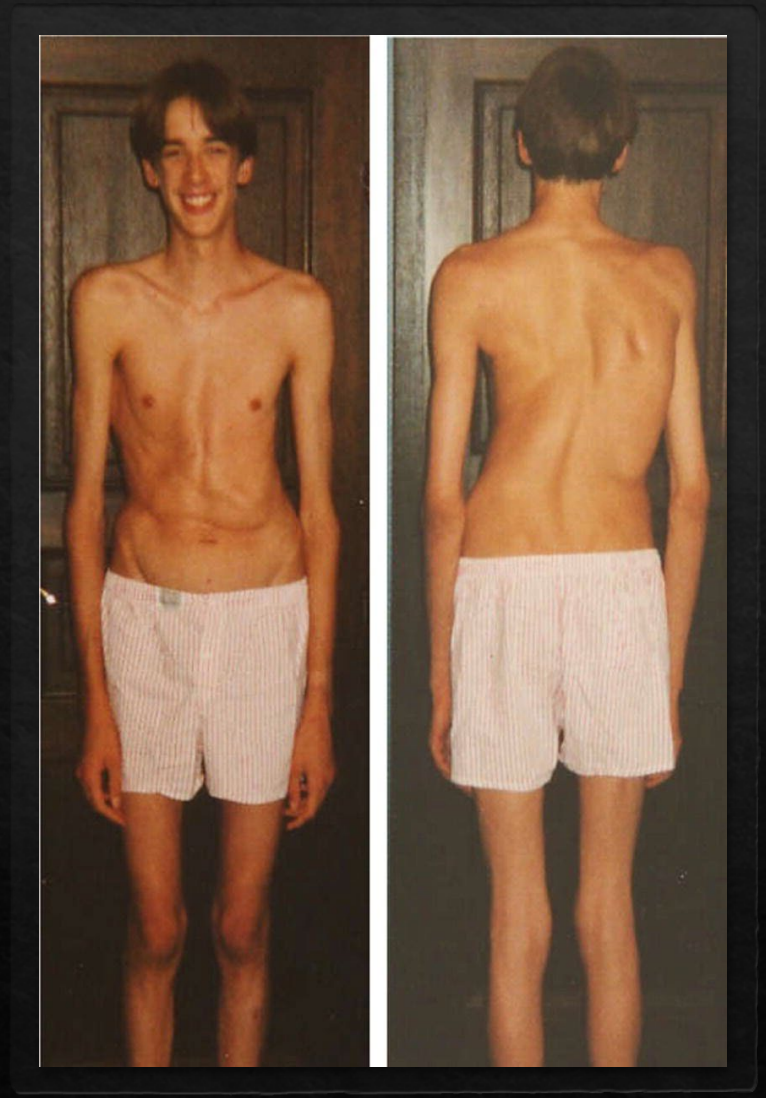
ETIOLOGY

- The most common form of genetic hyperhomocysteinemia results from production of a thermolabile variant of methylene tetrahydrofolate reductase (*MTHFR*) with reduced enzymatic activity (T mutation)
- **Vitamin deficiencies** – Increased blood levels of homocysteine may reflect deficiency of folate, vitamin B6, or vitamin B12. Plasma folate and B12 levels, in particular, are strong determinants of the homocysteine concentration.
- **Genetic factors**
- **Chronic kidney disease**
- **Drugs** & Smoking.

TESTING

Genetic testing for homocystinuria is not part of the routine newborn screen.

It is tested in adults only if there is a high suspicion such as first degree relative with homocystinuria or children and adolescents with characteristic physical findings, developmental delay, or cardiovascular disease or thromboembolism.



HISTOPATHOLOGY

- homocysteine-induced vascular injury include intimal thickening,
- elastic lamina disruption,
- smooth muscle hypertrophy,
- marked platelet accumulation,
- and the formation of platelet-enriched occlusive thrombi

HYPERHOMOCYSTINEMIA LEVELS

- moderate (15-30 micromol/L),
- intermediate (30-100 micromol/L)
- severe (>100 micromol/L)

- Moderate levels noted to be a risk marker for recurrent VTE

ACUTE TREATMENT

- It has not been shown that lowering homocysteine prevents cardiovascular events especially in an acute setting.
- Individual case studies have shown success with high flow oxygen, aspirin, clopidogrel, and glyceryl trinitrate sprays, in addition to betaine and folic acid treatment to help lower homocysteine levels

OUTPATIENT TREATMENT

- hydroxycobalamin and betaine, medical and biochemical assessments to maintain good metabolic control, and surveillance for possible complications.
- Betaine 100–250 mg/kg/day in children and 5–20 g/day in adults is used to increase systemic Met levels.
- referred to both a specialist in metabolic diseases and a nutritionist.
- A diet rich in fruits, vegetables, and low-fat dairy products and low in saturated and total fat also can lower serum homocysteine. It is also recommended to monitor for all aspects of renal disease including arterial blood pressure in patients with cobalamin related remethylation disorders

Other case reports

- In a research study done on stroke in young patients (Kelly P et al 2003) due to cystathionine beta-synthase deficiency patients were treated with warfarin, folic acid (1 mg/d), and pyridoxine (300 mg/d). Repeat B-mode carotid ultrasound at 5 weeks showed complete resolution of the intraluminal signal abnormality, consistent with dissolution of thrombus (see figure 2B). Repeat homocysteine measurement was 8 mol/L (Previously 279). Marked improvement occurred, with resolution of the sensory deficits and minimal residual weakness at 6 months(Kelly P et al 2003)

QUESTION # 1

QUESTION # 2

REFERENCES

- Robert S Rosenson, C Christopher Smith, Kenneth A Bauer. Overview of Homocystiene. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on June 01, 2020.)
- Kelly P, Furie K, Kistler J, et al.Stroke in young patients with hyperhomocysteinemia due to cystathionine beta-synthase deficiency. Neurology. 2003;60(2):275-279. doi: 10.1212/01.WNL.0000042479.55406.B3.
- Mazaheri, A., Mostofizadeh, N., & Hashemipour, M. (2017). Homocystinuria with Stroke and Positive Familial History. Advanced biomedical research, 6, 132. https://doi.org/10.4103/2277-9175.217215
- Ukachukwu, V., Idris, S., & McIlwee, A. (2012). Acute myocardial infarction in a young patient with hyperhomocysteinaemia. *BMJ case reports*, *2012*, bcr2012007489. https://doi.org/10.1136/bcr-2012-007489
- http://www.bimdg.org.uk/store/enbs//HCU_Dietetic_Management_Pathway_V1_April_2015_215380_12052015.pdf