51. MTHFR and homocysteine

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Q1: "Could someone explain what MTHFR is? Is it another blood clotting disorder like factor V Leiden?"
A1: MTHFR stands for Methylene-Tetra-Hydro-Folate-Reductase. Some individuals with the homozygous MTHFR mutation have elevated homocysteine levels. Elevated homocysteine levels are a risk factor for blood clots. The individual with the MTHFR mutation who have normal homocysteine levels are not at increased risk for clots. Thus, the MTHFR mutation by itself is not a clotting disorder.

Q2: "I'd like to know if MTHFR mutation can be hetero, as well as homo?"
A2: There are 3 scenarios: either one does not have the MTHFR mutation, or one is heterozygous (1 variant gene), or homozygous (2 variant genes).

Q3: "My sister was diagnosed with FVL and also found to be positive for MTHFR. Her doctor wants her to take extra folic acid. What is MTHFR and what is the treatment for it? Is it hereditary?"
A3: Is the sister heterozygous or homozygous for the MTHFR mutation? Only the homozygous mutation has been associated with elevated homocysteine levels. I never test for the MTHFR mutation. All I want to know is whether a person's homocysteine level is elevated. If it is elevated then I treat the patient as described below. Yes, the MTHFR mutation is hereditary - same inheritance pattern as factor V Leiden (see Q/A 12).

Q4: "I am FVL hetero, MTHFR hetero.I was told MTHFR increases your homocysteine levels and can be treated with vitamin B therapy. Now I take vitamin Bs."
A4: Almost half of the population is "MTHFR hetero" - it is nothing abnormal. The heterozygous MTHFR mutation (= 1 "abnormal" gene) does not lead to increased homocysteine levels. It is the homozygous MTHFR mutation (2 "abnormal" genes) that is associated with higher homocysteine levels. However, it is the fasting homocysteine level that counts, independent of whether the patient has the MTHFR mutation or not. If an individual's fasting homocysteine level is normal, there is no need for vitamin B or folate therapy - even if the patient has the homozygous MTHFR mutation.

MTHFR stands for Methylene-Tetra-Hydro-Folate-Reductase. MTHFR is an enzyme, which we all have in the cells of our body. It is needed to metabolize and get rid of homocysteine. High homocysteine levels are a risk factor for blood clots in the veins (DVT, PE) or arteries (heart attack, stroke, arteriosclerosis). Some people have a variant of this enzyme, which is called "thermolabile MTHFR" or C677T MTHFR. It is due to a single mutation of the MTHFR gene. This variant does not metabolize homocysteine as well as the normal MTHFR enzyme, and blood homocysteine levels in individuals with this variant enzyme may, therefore, be slightly higher than in individuals with the normal enzyme.

The MTHFR mutation is extremely common:

- 44 of the population have the normal enzyme
- 44 % are heterozygous for the mutation (i.e. have 1 variant gene). These individuals have some normal enzyme and some of the thermolabile variant of the enzyme.
- 12 % are homozygous for the mutation (i.e. have 2 variant genes). All of these individuals' enzyme is the thermolabile variant.

Presence of the homozygous thermolabile MTHFR mutation is only one of various reasons why homocysteine levels can be elevated. Other reasons are vitamin B and folate deficiency and renal failure. Often we do not know why levels are elevated. Some studies reported that the homozygous thermolabile MTHFR mutation is associated with arterial clots. However, an overview of all studies concluded that this is NOT so (ref 1). Earlier studies on the association of the homozygous MTHFR mutation and venous blood clots (DVT, PE) have been inconsistent: some studies found a slight association, others none at all. A recent large analysis of all studies published showed that, in the U.S., the MTHFR mutation is NOT a risk factor for venous clots (ref 2). Finally, a recent analysis of all published studies on pregnancy complications and MTHFR mutation also showed, that the mutation is NOT a risk factor for pregnancy complications (ref. 3).

A normal homocysteine level is often defined as one being less than 13.0 micromol/L. The higher the level, the higher the risk for clots. Levels can be lowered by taking a multiple vitamin with a high content of folic acid (for example 400

mcg = 0.4 mg), vitamin B6 (= pyridoxine; for example 25 mg) and B12 (= cobalamin; for example 1 mg). Often folate treatment alone (dose: 0.4-5 mg per day) lowers homocysteine levels into the normal range. However, several publications in the last several years have consistently shown that lowering homocysteine levels does NOT change the risk for future blood clots. Thus, there is at present no good reason to treat an individual with elevated homocysteine levels with vitamin B6, vitamin B12, or folic acid , at least not a person with only slightly or moderately elevated levels (say, levels below 30 micromol/L). Whether individuals with more significantly elevated homocysteine levels may benefit form lowering of homocysteine levels is not know. Therefore, I have the tendency to recommend treatment to these individual with a combination pill of vitamin B6, vitamin B12, or folic acid (for choices, see table).

1000 mcg $20.69 Yes
1000 mcg $12.49 –
2.2 mg 25 mg 500 mcg $14.01 No

Brand name	Folic Acid	Vitamin B6 = pyridoxine	Vitamin B12 = cyanocobalamin	Approximate Monthly Cost	Generic available
Foltx®	2.5 mg	25 mg	1000 mcg	$20.69	Yes
Folbee*	2.5 mg	25 mg	1000 mcg	$12.49	-
Folgard® Rx 2.2	2.5 mg	25 mg	500 mcg	$14.01	No

*generic for Foltx®

Approximately 2 months after starting vitamins a homocysteine level should be checked again to make sure it has decreased into the normal range.
See also Q/A 77 “Homocysteine”.

Personal comment:

I never obtain the genetic test for the MTHFR mutation in the patients I see. It is the homocysteine level that counts. While the MTHFR mutation can be associated with elevated homocysteine levels, the MTHFR by itself is, in the U.S. where food is fortified with folic acid, not a risk factor for arterial clots, venous clots, or pregnancy complications.

References:

1. Circulation;1998:2520-2
2. Klerk M. JAMA 2002;288:2023-2031
3. Rey E. Lancet 2003;361:901-908.
4. den Heijer M. J Thomb Haemost 2005;3:292-9