KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Impaired Methylation - Part Four

Now let's talk about treatment. We discussed this already at some length in the B12 and folate-deficiency anemia presentation. There has been a recent trend toward using high-dose methyl donors in supplement form to treat methylation-related problems. We've done this ourselves with our patients for the past few years, and still do in some cases. However, after more research, I've become somewhat more conservative in my approach. As we discussed in the other presentation, there is some evidence that suggests that overmethylation may be detrimental, and the scientific literature does have examples of overmethylation associated with adverse effects, primarily immune dysregulation. I'm concerned that we don't really have enough research on the effects of long-term supplementation with high-dose methyl donors.

Methylation status depends on diet and lifestyle inputs, and I think diet and lifestyle change is the safest option given the research that we do have on overmethylation, and the lack of research on long-term safety of taking these methyl donors at really high doses.

Nutrients

Methionine	Niacin
Cysteine	Pyridoxine
Taurine	Folate
DHA	Vitamin B12
Zinc	Betaine (TMG)
Magnesium	Choline
Potassium	Sulfur
Riboflavin	

All of the nutrients on this slide are involved in the methylation cycle, and all of them can be obtained from food in a nutrient-dense diet. We have created a patient handout that shows the foods that are highest in these nutrients that we give to patients who have methylation-related issues, and we will typically use this as a starting place and then retest and see if we've been able to make progress. If not, then we might consider short-term supplementation with high-dose methyl donors.

In those cases, if the patient is already on a nutrient-dense diet and still has issues and abnormal labs, we may do a supplement protocol. If you do supplement, it is important to avoid folic acid, which is a synthetic compound used only in dietary supplements and food fortification.

The form of folate that can enter the main folate metabolic cycle is tetrahydrofolate or THF. Unlike natural folates, which are metabolized to THF in the mucosa of the small intestine, folic acid undergoes initial reduction and methylation in the liver, where a conversion to the THF form requires dihydrofolate reductase. Unfortunately, a lot of human beings have a relatively low activity of dihydrofolate reductase in the liver, and combined with a high intake of folic acid from fortified foods, this may result in unnatural levels of unmetabolized folic acid entering the systemic circulation. Several studies have shown that excess unmetabolized folic acid is associated with several diseases and conditions, including cancer, depressed immune function, deterioration of central nervous system function, anemia, and cognitive impairment. I wrote an article about this a while back that you may have seen, and we're going to link to it in the resources section.

The best forms to supplement with are 5-MTHF or folinic acid, 5-formyl-THF. Remember, 5-MTHF is a cofactor for methionine synthase, which converts homocysteine back into methionine. I prefer starting with a lower dose of 200 to 400 mcg per day of 5-MTHF, rather than the much higher doses—up to 5 to 10 mg—that are sometimes used. Note that a substantial number of people experience side effects even with lower doses of 5-MTHF, including anxiety, agitation, insomnia, and overstimulation. In some cases, these will pass after a short period of time, but in other cases, we've had patients who are just not able to tolerate 5-MTHF, even at a very low dose. In these cases we will use folinic acid at a dose of 800 mcg per day, which is much better tolerated than 5-MTHF, and typically works pretty well for normalizing folate. You just have to experiment a bit here because some patients do really well on 5-MTHF and don't get great results with folinic acid, and for others, it is the other way around.

Also, some studies have shown that folinic acid may support cerebral folate levels in specific circumstances where autoantibodies to folate transport proteins at the blood-brain barrier are present.

Whichever you choose, make sure to retest after 60 days to determine whether the intervention is working. Once the mechanisms have been addressed, consider transitioning to a dietary approach for all the reasons we discussed earlier. If the patient is unable to maintain their folate levels just with diet alone, there is some uncertainty now about what to do. We have to weigh the risk of high homocysteine, which is an inflammatory protein associated with cardiovascular disease and cognitive disorders such as Alzheimer's, versus the risk of supplementing long-term with higher

doses of methyl donors, which as you know, has been shown to have some adverse effects in certain studies.

As far as I can tell, the best option in these cases is probably to supplement, but use the lowest effective dose, and then continue to address mechanisms that are known to impair methylation, which we have discussed in this presentation. Hopefully, if you do that, the patient will be able to maintain normal folate levels with diet alone or maybe with a very minimal dose of methyl donor supplement.

Okay, that's it for now. See you next time.