ABSTRACT:

Objectives:

MTHFR defects are known to include a large portion of the healthy human population. The aim of this study is to determine if the incidence of MTHFR defect in the CFS/FMS population is different than the general population, and if specific intervention to treat such defects improves outcomes over standard integrative naturopathic therapy this population.

Design:

Active comparator trial

Measures:

Laboratory analysis of 88 previously diagnosed CFS/FMS patients as compared to population matched controls.

Results:

Incidence of the medically correlated gene variants for MTHFR (C677T and A1298C) in the total population are estimated to be between 36 – 49 % for heterozygotes, 10-12% for homozygotes and 10-20% for compound heterozygotes [1,2,4]. While Harmon DL, et.al. [3] originally published no correlation between CFS and a higher incidence in MTHFR variation in 1997 our clinical experience seemed to point to a different correlation. We selected 88 patients with a prior diagnosis of FMS or CFS (based on commonly accepted diagnostic criteria) and tested them for the C677T and A1298C gene variants. We then treated them in a manner consistent with an active comparator trial based on their MTHFR status and compared their therapeutic outcomes after the addition of MTHFR specific therapy to the standard integrative naturopathic therapy they had been receiving.

Conclusions:

MTHFR incidence in the CFS/FMS patient was significantly higher than general population averages with a different distribution of gene defect patterns. The addition of MTHFR specific therapy based on lab findings yielded a significant improvement in outcome as compared to the standard integrative naturopathic therapy in an active comparator trial. These data underscore the importance of proper diagnosis and management of the MTHFR defect group in the CFS/FMS patient population.
Introduction:

MTHFR defects are known to include a large portion of the healthy human population. The aim of this study was to determine if the incidence of MTHFR defect in the CFS/FMS population is different than the general population. Earlier publication indicated that in the case of CFS this was not the case. Our clinical experience pointed to a different possibility, but no data had been published in the CFS / FMS population since Harmon in 1997 [3].

In addition to the data on incidence we endeavored to quantify, via an active comparator trial design, if patients already being treated in an integrated naturopathic program would have improvement in outcomes over baseline with specific therapy for their methylation defect.

Materials and Methods:

Incidence of MTHFR mutations in the CFS / FMS population versus controls:

Laboratory analysis of 88 previously diagnosed CFS/FMS patients for the two common gene variants of MTHFR (C677T and A1298C) as compared to population matched controls.

Inclusion Criteria - Active Comparator Treatment Arm:

- Prior diagnosis with CFS or FMS
- Diagnosis with any MTHFR defect
- Able to include methyl support in their therapeutic plan
- Able to undergo and assess a minimum of 90 days therapeutic intervention

Signs and symptoms assessed regarding improvement or aggravation in the active comparator trial:

- Patient responses to previously validated assessments for CFS/FMS [5,6] which include fatigue, sleep disorder, myalgia, arthralgia, neuralgia, cephalgia, cognitive dysfunction, immune status (acute infections), mental emotional status and other factors.

Active Comparator:

Baseline existing integrated treatment for CFS or FMS

- H&P; Lab and Imaging as necessary; appropriate therapy for underlying disorders.
- Multi-factorial therapies including nutrient, diet, hormone, inflammatory, sleep, movement and other interventions.
- No new diagnosis of co-morbid pathology to treat.
Discussion:

Methylation – some important biological roles [11-14]:

- Synthesis of new DNA and RNA. Also plays a role in epigenetic alteration of certain DNA to prevent its expression, and in producing myelin for the brain and nervous system.
- Contributes to determining the rate of glutathione synthesis by governing how much homocysteine is diverted into the transsulfuration pathway.
- Control the overall sulfur metabolism of the body including cysteine, taurine and sulfate.
- Key for the synthesis of coenzyme Q-10 and l-carnitine.
- Supports formation of Serotonin, Dopamine, Norepinephrine and Epinephrine
- Supports MAO and COMT enzyme systems as well as the reduction of Histamine (which is then excreted via the MAO system).

  - For the above reasons two of the most significant effects of slow methylation are that neither the immune system nor the detox system can operate properly. If methylation is slowed or blocked infections and toxins can build up in the body.

![Methyl Cycle – Sulfur AA Interactions](image)
Results - Incidence:

Incidence of the medically correlated gene variants for MTHFR (C677T and A1298C) in the total population are estimated to be between 36 – 49% for heterozygotes, 10-12% for homozygotes and 10-20% for compound heterozygotes [1,2,4]. While Harmon DL, et.al. [3] originally published no correlation between CFS and a higher incidence in MTHFR variation in 1997 our data show not only a difference in incidence but also in distribution of defect incidence from the control population to the study population. There are significant differences in that the incidence of heterozygous defects are 40% less for A1298C and 70% less for C677T in the CFS / FMS population while there is an increased incidence of compound heterozygous defect of 53% and Homozygous C677T of 44%. Homozygous A1298C was not significantly different from the control population.

<table>
<thead>
<tr>
<th>Incidence Data:</th>
<th>Hetero A1298C</th>
<th>Hetero C677T</th>
<th>Compound Hetero</th>
<th>Homo A1298C</th>
<th>Homo C677T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study n = 88</td>
<td>23</td>
<td>12</td>
<td>19</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>% CFS/FMS Participants</td>
<td>26</td>
<td>13</td>
<td>23</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>% Normal population</td>
<td>43</td>
<td>43</td>
<td>15</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>% Incidence Difference</td>
<td>-40</td>
<td>-70</td>
<td>+53</td>
<td>-1</td>
<td>+44</td>
</tr>
</tbody>
</table>

Active comparator intervention:

Initial Therapeutic Considerations based on previously published data [7-10]:

1: Methyl Donor Support:

- Methyl B-12 1-5 mg SL / QD (Or 3-5 mg IM weekly)

2: Collateral Pathway Support:

- Pyridoxal-5-phosphate 50 – 100 mg BID
- Betaine HCl 3 – 9 grams divided doses with meals - NAC 500mg BID

3: Direct 5-MTHF Support:

- 5-MTHF ramp up 1 to 5 or 15 mg QD (or IM 5 mg 1-3X weekly)
- B-2 & B-3 as obtained in a high potency b-complex.

**NOTE: Less supplementation may be required for maintenance.
Forms of Folate:

- Folic Acid requires DHF reductase
- Folinic Acid / Leukovorin (formyl-THF) No DHF reductase required
- 5-Methyltetrahydrofolate

(Graphics) [Link](http://web2.iadfw.net/uthman/nutritional_anemia/nutritional_anemia.html)

Therapeutic interventions made:

Primary intervention was the addition of MTHFR specific oral methyl support [7-10]:

Note: Some patients required additional collateral pathway support (see above for agents).

- Heterozygotes:
  - Calcium Folinate + Methyl B-12 [5 mg b-12 and 800 mcg folinic acid]
  - B-Complex

- Homozygotes:
  - 5-MTHF [2 – 15 mg/d]
  - Methyl B-12 [5-10 mg]
  - "Methyl-Support Multi" [ Riboflavin 5'-Phosphate 90 mg / Pyridoxal 5'-Phosphate 45 mg / L-5-MTHF 3 mg / Methylcobalamin 3 mg / Trimethylglycline 1,800 mg]
- Compound Heterozygotes:
  - Originally same as heterozygotes.
  - Anecdotal reports of slow progress caused a change to treatment with the same interventions as homozygotes which by patient report and physician assessment yielded improved response.

Parenteral (IM and IV) Options:
  - 5-10 mg of 5MTHF and 3-10 mg Methyl B-12 combined with 1-2 mL B-100 (parenteral B-complex) in a suitable base solution administered IM or IV twice weekly for 3-6 weeks then weekly for 12 weeks. This was followed by appropriate oral prescription.

All patients were counseled regarding dietary support; Data on food sources? [15]
  - Spinach, Chinese cabbage, lettuce, cauliflower, and broccoli contained more than 50 μg of 5-MTHF /100g
    - Less than 25 μg /100 g was found in potatoes, carrot, white cabbage, green and yellow pepper.
  - Individual vegetables differed in the folate retention during their boiling under constant conditions.
    - The highest retention was found in Brussels sprouts, cauliflower, and broccoli. After 8 min boiling more than 75% of the initial amount of 5-MTHF remained in these vegetables.
    - Lower values of 5-MTHF retention, between 37% and 52% of their initial content, were found in spinach, savoy cabbage, and carrot.

<table>
<thead>
<tr>
<th>Sample Matrix</th>
<th>Average 5MTHF μg/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asparagus, Cooked</td>
<td>114</td>
</tr>
<tr>
<td>Asparagus, Cooked</td>
<td>117</td>
</tr>
<tr>
<td>Bananas</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Peas</td>
<td>48</td>
</tr>
<tr>
<td>Bok Choy</td>
<td>48</td>
</tr>
<tr>
<td>Broccoli</td>
<td>48</td>
</tr>
<tr>
<td>Brussels Sprouts</td>
<td>48</td>
</tr>
<tr>
<td>Celery</td>
<td>48</td>
</tr>
<tr>
<td>Clementine</td>
<td>48</td>
</tr>
<tr>
<td>Collards</td>
<td>48</td>
</tr>
<tr>
<td>Dates</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Green Cabbage</td>
<td>17</td>
</tr>
<tr>
<td>Green Leaf Lettuce</td>
<td>36</td>
</tr>
<tr>
<td>Green Peppers</td>
<td>36</td>
</tr>
<tr>
<td>Pinto Beans, Cooked</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Pinto Beans, Dried</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Frises</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Red Cabbage</td>
<td>32</td>
</tr>
<tr>
<td>Red Potatoes</td>
<td>14</td>
</tr>
<tr>
<td>Romaine Lettuce</td>
<td>32</td>
</tr>
<tr>
<td>Strawberries</td>
<td>17</td>
</tr>
<tr>
<td>Sweet Onion</td>
<td>6</td>
</tr>
<tr>
<td>Swiss Chard</td>
<td>61</td>
</tr>
</tbody>
</table>
Results – Active Comparator:

We selected between 22 and 50% of the original patients to include in the active comparator arm. We then treated them in a manner consistent with an active comparator trial based on their MTHFR status (see above) and compared their therapeutic outcomes after the addition of MTHFR specific therapy to the standard integrative naturopathic therapy they had been receiving. Of note, all patients had, as a portion of their integrated naturopathic therapy prior to the study, received intravenous therapy including B-complex and 3-10 mg Methyl B-12 on at least 10 occasions. All were on a high quality multivitamin supplement.

Based on validated outcomes measurements [5, 6] the change in outcomes ranged between an increase in positive outcome between 55 and 75% (table below).

<table>
<thead>
<tr>
<th>Active comparator</th>
<th>Hetero A1298C</th>
<th>Hetero C677T</th>
<th>Compound Hetero</th>
<th>Homo A1298C</th>
<th>Homo C677T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention % (of n)</td>
<td>22</td>
<td>25</td>
<td>47</td>
<td>50</td>
<td>27</td>
</tr>
<tr>
<td>% outcome improvement</td>
<td>+ 55%</td>
<td>+ 75%</td>
<td>+ 56%</td>
<td>+ 56%</td>
<td>+ 71%</td>
</tr>
</tbody>
</table>

Conclusions:

Unlike data previously published for CFS our data indicate that a significant difference in incidence and in distribution of defect incidence from the control population to the study population of CFS / FMS patients exists.

Given the wide ranging importance of methylation for human health and the high incidence of methylation defects in the CFS / FMS population a strong association can be made as to partial causality in the very multi-factorial illnesses characterized as CFS and FMS.

While refinements in interventions and testing will undoubtedly be made our interventional data show that significant improvement in patient outcomes can be achieved in the CFS / FMS population by testing and treating methyl cycle defects. Some patients require higher and longer loading doses of nutrients before achieving maintenance dosing and some (typically over 50 years of age and / or very toxic) required very slow introduction of methyl support to reduce detoxification reactions. Of anecdotal note only 33% of the compound heterozygous and C677T homozygous groups experienced detoxification reactions (increased transient headache, arthralgia or myalgia and fatigue) which resolved with dose adjustments or simply time in treatment. All subjects who reported detoxification reactions refused to stop treatment due to feeling positive change in the midst of such reactions.

More study is needed but it appears clear from these data that early testing and intervention for MTHFR defects in anyone with signs and symptoms in the CFS / FMS spectrum is clearly indicated.
References: