Fatigue was measured through patient reported outcome composite scores from the FACIT-F and FSS tests. Presence of the polymorphisms were assessed by extracting and analyzing patient blood samples and running TaqMan qPCR.

RESULTS

Table 1. Chi-Square Contingency Test for Complete Patient Cohort and Fatigue Symptoms

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>No Fatigue</th>
<th>Fatigue</th>
<th>Row Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFE Wild Type</td>
<td>14</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>HFE Polymorphism</td>
<td>18</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Column Totals</td>
<td>32</td>
<td>19</td>
<td>Total = 51</td>
</tr>
</tbody>
</table>

Table 2. Chi-Square Contingency Test for Chronic Inflammation Patients and Fatigue Symptoms

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>No Fatigue</th>
<th>Fatigue</th>
<th>Row Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFE Wild Type</td>
<td>11</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>HFE Polymorphism</td>
<td>11</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Column Totals</td>
<td>22</td>
<td>13</td>
<td>Total = 35</td>
</tr>
</tbody>
</table>

Table 3. Chi-Square Contingency Test for NAFLD Patients and Fatigue Symptoms

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>No Fatigue</th>
<th>Fatigue</th>
<th>Row Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFE Wild Type</td>
<td>7</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>HFE Polymorphism</td>
<td>13</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>Column Totals</td>
<td>20</td>
<td>32</td>
<td>Total = 52</td>
</tr>
</tbody>
</table>

Figure 1. Increased Iron Uptake

Liver cell
HFE protein bound to IRP
Hepcidin production turned off
Binds to ferritin
Hepcidin produced
Excess iron flows in and is absorbed by enterocytes

Figure 2. Iron Overload Coping Mechanism

Increased Basal Ganglia Iron
Increased presence of iron, perhaps preventing inflammation associated anemia by corresponding to higher platelet counts, positively correlates to presence of HFE mutation in these data.

FURTHER STUDY

• Future studies should investigate activity in the context of HFE and chronic metabolic syndrome, perhaps by comparing activity scores and polymorphisms (HAP scores)
• Increase in cohort size, patient diversity, and age range

RESULTS

• Two-Sample T-test assuming Unequal Variances indicated no statistically significant mean difference between the HFE polymorphism and the WAIS IV Arithmetic test (p = 0.154) or Digit Span test (p = 0.310) in the NAFLD cohort.

Results of Chi-Square Tests:

• χ² analysis reveals linkage between HFE polymorphism and fatigue in complete patient cohort (χ² = 4.31, p = 0.03) (Table 1)
• χ² analysis reveals linkage between HFE polymorphism and fatigue in patients with chronic inflammatory conditions (χ² = 4.19, p = 0.04) (Table 2).

Results of Spearman Correlation with HFE Gene:

• Symptom of General Pain: 0.355
• WAIS IV Digit Span Forward Score: 0.357
• Platelet Count: 0.500

DISCUSSION

• In all cohorts, Chi-Square Contingency Tests showed linkages between HFE Polymorphisms and absence of severe fatigue.
• Increased presence of iron, perhaps preventing inflammation associated anemia by corresponding to higher platelet counts, positively correlates to presence of HFE mutation in these data.
• It is possible that protection from fatigue may result in more activity, which in turn may have a protective effect against chronic metabolic disease.
• Odds Ratio value below 1, suggests the HFE gene is protective from reported fatigue and NAFLD.
• No statistically significant Spearman associations observed with WAIS IV Arithmetic Scores and HFE polymorphisms, but with Digit Span Forward score only, therefore iron oxidative stress may likely impact working memory.

METHODS

• Mild cognitive dysfunction was measured through patient scores on the working memory subsets in the Wechsler Adult Intelligence Scale - Fourth Edition - Digit Span and Arithmetic.
• Fatigue was measured through patient reported outcome composite scores from the FACIT-F and FSS tests.
• Presence of the polymorphisms were assessed by extracting and analyzing patient blood samples and running TaqMan qPCR.
• Statistical analyses of Chi-Square contingency tests, Spearman correlation, T-test, and Mann-Whitney U Test were performed to observe associations in data.

PURPOSE OF STUDY

The purpose of conducting this study is to investigate whether HFE haploinsufficiency contributes to the subtle perturbation of iron metabolism, causing measurable change in fatigue and mild cognitive dysfunction in chronic metabolic disease, such as NAFLD, in patients aged 21-68.

BACKGROUND

• Hereditary hemochromatosis is a genetic disorder that causes the body to absorb iron excessively (Figure 1), leading to oxidative damage (U.S. National Library of Medicine).
• Mutations at the rs1800562 and rs1799945 loci in the HFE gene on chromosome 6, and rs38179872 focus in the IRP gene on chromosome 3, are nonsynonymous polymorphisms that contribute to increased risk of hereditary hemochromatosis (Mariati et al).
• The brain is particularly susceptible to oxidative stress due to its high iron requirement and easy passage of iron through the blood-brain barrier.
• Increased basal ganglia iron was seen to be associated with worse performance in working memory (Bartzokis et al).

• Haploinsufficiency of the HFE gene could be the reason for heterozygote advantage, leading to a coping mechanism against inflammatory conditions such as iron deficiency anemia (Distante et al).
• Or, oxidative stress and damage to erythrocytes induced by iron overload could contribute to abnormal fatigue experienced (Richards et al) (Figure 2).
• The patients in the data set are part of the Non-alcoholic Fatty Liver Disease (NAFLD) study, a disorder part of the chronic metabolic syndrome that includes diabetes and obesity. Hereditary Hemochromatosis can contribute to the development of NAFLD.

• Presence of HFE mutation in these data was associated with milder fatigue, lending a coping mechanism against inflammatory conditions such as iron deficiency anemia (Distante et al).
• Hereditary hemochromatosis is a genetic disorder that causes the body to absorb iron excessively (Figure 1), leading to oxidative damage (U.S. National Library of Medicine).
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