We have previously shown profound folate deficiency with high homocysteine (HC) levels, causing peripheral neuropathy and megaloblastic anemia in cough mixture abusers. Damage may also be seen in the central nervous system and the fetal neural tube. Community screening among cough mixture abusers is needed.

With informed consent, 57 cough mixture abusers (60 mL daily × 2 months; 46 men, 11 women; median age 32.1) and 47 other substance abusers (controls, 28 men, 19 women; median age 31) were interviewed from five out-reach clinics. There were more men among the cough mixture abusers (p=0.021) but other social features (employment, living conditions, marriage) were matched between the two groups. Blood samples were frozen and batch assayed for total HC and plasma homocysteinemic acid (MMA) levels. Normal reference ranges were derived from 20 samples from volunteers stored and processed in parallel. The study was approved by the institution review board.

Among the cough mixture abusers, 16 were poly-substance abusers (benzodiazepine=12, heroin=3, ice/alcohol/cannabis/ecstasy=1 each, undeclared=2). The content of cough mixture is regulated in Hong Kong (www.pshd.gov.hk/eps/webpage.jsp) and both codeine (n=33) and dextromethorphan (n=18) were abused. Some subjects reported combined usage of the two types (n=5) and use of codeine pills (n=1). The median daily volume of cough mixture consumed was 290 mL (range 50-1500 mL). The controls abused a variety of substances (heroin=22, benzodiazepine=7, alcohol=9, ketamine=7, cannabis=6, ecstasy=5, ice=4, volatile solvent=1, others=2) and 15 of them were polysubstance abusers.

Cough mixture abusers had higher red cell folate (557 vs 786 nmol/L, p<0.001) and serum vitamin B12 levels (193 vs 282 pmol/L, p<0.001) than controls. They also had higher platelet counts (279 vs 230x10^11/L, p=0.015) but comparable hemoglobin concentration (14.3 vs 13.7 g/dL, p=0.07) and mean cell volume (90.0 vs 90.2 fL, p=0.42). The incidence of folate and vitamin B12 deficiencies among cough mixture abusers was 39% (control 63.3%, p<0.001, RR=6.0) and 21% (control 0%), respectively. There was a strong correlation between folate and vitamin B12 levels (r=0.004, R=0.28) and eight patients had concomitant deficiencies in both. The folate-deficient cases consumed a greater volume of cough mixture (481 mL vs. 188 mL, p=0.006).

Although codeine and dextromethorphan are both opiates, folate (p=0.004) and vitamin B12 (p=0.004) levels were lower, and platelet counts higher (p=0.003) among cough mixture abusers than among heroin abusers. These values showed no difference between codeine and dextromethorphan abusers. An analysis of metabolites showed no statistically significant differences between cough mixture abusers and controls with regards to HC (21.1 vs 22.5 umol/L, p=0.18) and MMA levels (0.41 vs 0.27 pmol/L, p=0.46). However, when patients with low Fo and B12 were compared against the rest of cohort, folate-deficient patients had higher HC levels. On the other hand, MMA levels were not increased in folate or vitamin B12-deficient cases (Table 1).

Macrocytosis (MCV>96 fL) was a poor marker of folate deficiency. Among 18 macrocytic patients (range 96.2-109.8 fL), only 9/18 were cough mixture abusers, and 7/18 had low folate levels. The cough mixture abusers reported psychosis (n=25), numbness (n=23), weakness (n=11), dizziness (n=6) and dental carries (n=49). Patients reporting numbness consumed more cough mixture (470 mL vs. 202 mL, p=0.004) and had lower vitamin B12 level (223 vs 228 pmol/L, p=0.039), while those with psychosis had lower vitamin B12 levels (227 vs 285 pmol/L, p=0.031), higher HC (24.1 vs 18.4 pmol/L, p=0.08) and higher consumption of cough mixture (419 mL vs. 223 mL, p=0.04). There was no symptomatic association with folate findings.

Our prospective data showed that cough mixture abuse is associated with low folate levels. This is unrelated to concomitant drug use or the type of cough suppressant (dextromethorphan or codeine) abused, and may be dose-dependent. The low folate levels were also unrelated to sugar consumption (absent in codeine pills). Many patients also had low vitamin B12 levels, usually accompanied by low folate levels. Metabolite assays in our published hospital-based study had shown that this is sec-

**Table 1. Metabolite and hematologic parameters in folate and vitamin B12 deficient patients.**

<table>
<thead>
<tr>
<th>HC (µmol/L)</th>
<th>MMA (µmol/L)</th>
<th>B12 low (µmol/L)</th>
<th>Hb (g/dL)</th>
<th>WCC (×10^12/L)</th>
<th>Platelets (×10^12/L)</th>
<th>MCV (fL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low red</td>
<td>25.29 ± 0.14</td>
<td>14.3 ± 0.65</td>
<td>92.9 ± 1.7</td>
<td>14.1 ± 0.28</td>
<td>257.2 ± 10.5</td>
<td>0.94</td>
</tr>
<tr>
<td>(n=25)</td>
<td>p&lt;0.002</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p=0.006</td>
<td>p=0.028</td>
<td></td>
</tr>
<tr>
<td>vs. normal</td>
<td>RR=6.3</td>
<td>(2.19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low vitamin</td>
<td>25.6 ± 0.14</td>
<td>14.3 ± 0.65</td>
<td>88.9 ± 1.7</td>
<td>261 ± 0.7</td>
<td>290 ± 0.9</td>
<td>0.94</td>
</tr>
<tr>
<td>(n=10)</td>
<td>p=0.75</td>
<td>p=0.07</td>
<td>p=0.10</td>
<td>p=0.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Letters to the Editor**
ondary to severe folate deficiency. Similarly, in this community-based cohort, patients with low vitamin B12 levels had significantly raised levels of HC (characteristic of folate pathway blockade) but not significantly raised MMA. Finally, we found a novel but unexplained thrombocytosis in cough mixture abusers.

Due to voluntary participation, our study cases may not be representative of all cough mixture abusers. We also failed to identify dietary, genetic and lifestyle risks for folate deficiency present in 6% of the controls. However, our prospective, community-based study showed that clinical symptoms and hematologic parameters are a poor guide to folate deficiency in at-risk populations. Hence, prospective screening and vitamin supplementation may be needed.

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References


ERRATA CORRIGE

In an article published during 2004, an author name was erroneously written (V. LeCam-Duchez, instead of V. Le Cam-Duchez); correct citation becomes: