Serum magnesium profile in heroin addicts: according to psychiatric comorbidity

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Abstract. Psychiatric comorbidity in heroin addiction can modify both the biological pattern and clinical course of this disorder. Because of the role of magnesium in neurotransmission and its specific patterns in some psychiatric conditions, such as depression and schizophrenia, we studied a sample of heroin dependent subjects, with and without psychiatric comorbidity. A sample of 162 drug addicts (123 men and 39 women, mean age 32.3 ± 6.7) was diagnosed for the presence of psychiatric comorbidity with DSM IV criteria. They were subsequently divided in 4 subgroups: No comorbidity, Anxiety Disorders, Mood Disorders, Personality Disorders. Differences in serum magnesium level between the groups were analysed with the Anova method, with age as covariate. Results show that serum Mg²⁺ levels are significantly higher in patients with heroin dependence and personality disorders compared to patients with depression comorbidity and without comorbidity. Psychiatric codiagnosis significantly modifies Mg²⁺ levels in this drug dependent sample. Gender modifies Mg levels in no comorbid subjects so that females show significantly lower Mg²⁺ levels compared to males. The presence of psychiatric comorbidity abates this difference.

Key words: psychiatric comorbidity, addiction, magnesium

Serum magnesium levels have been studied in psychiatric disorders because of the important magnesium involvement in neurotransmission. Mg²⁺ levels are higher in mood disorders than in healthy controls [1, 2] and are not related to the diagnostic subtype of depression or to disease phase [3].
As regards its role in the pathophysiology of depression, a direct effect on the blood-brain barrier and a stimulating effect on the Na/K-ATPase activity were demonstrated [4], together with indirect effects, including antagonistic to N-methyl-D-aspartate and agonistic to GABA.
On the contrary, reduced Mg²⁺ levels were found in schizophrenia. A pathogenetic hypothesis about this disorder, involving a dysfunction of the hypothalamic digoxin modulation on conscious and subliminal perception, was recently advanced [5]: low magnesium levels could be a marker of this condition. Moreover, some authors [6] considered decreased erythrocyte Mg²⁺ level among the main biological markers of acute paranoid schizophrenia. A similar reduction in intracellular magnesium levels has been found in autism [7].
To date, no information is available about Mg²⁺ levels in personality disorders or in borderline states. In the diagnostic field of heroin dependence, basic Mg²⁺ serum levels are not significantly different from healthy subjects’ levels [8], and are not changed.

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before or after detoxification. The clinical interest of this cation is related to its potentiating effect on opiate analgesy. Therefore, magnesium sulphate has been proposed in pure and polysubstance opiate detoxification, to prevent the withdrawal excitatory effects [9].

As regards to double-diagnosis patients (drug dependency and psychiatric disorders), no data are available at present about serum magnesium levels, even though psychiatric comorbidity is known to produce several metabolic differences in drug dependent subjects. The aim of this study was to assess the effects of psychiatric comorbidity on serum magnesium levels in heroin addicts.

Material and methods

Data concerning a consecutive sample of 162 drug addict subjects presented for a disintoxication therapy at the Psychiatric Day Clinic and Drug Addiction of the “A. Gemelli” Hospital were evaluated.

At the time of hospitalization, most patients used a substitutive therapy with methadone low dose (10-20 mg Epithadone per os/die) and the patients were not HIV positive. Data were collected at first assessment, before starting detoxification and other therapies. The study included 39 women and 123 men aged 17-51 (mean age 32.3). Socio-demographic characteristics of the sample are presented in table 1.

Each patient had been previously exposed to a clinical psychiatric evaluation and estimated with the SCID I-II [10, 11] questionnaire in order to characterize the psychiatric comorbidity presence.

Based on the results of the questionnaire, the subjects were divided into four subgroups: the patients without drug addiction comorbidity; the patients with Anxiety Disorder comorbidity (inclusive of the DSM-IV classes); the patients with Mood Disorder comorbidity (this subgroup includes whether Dysphoria Disorder or Major Depression; the patients with personality disorder comorbidity (mostly in accordance with the cluster B and in particular Borderline Disorder).

Table 2 shows the distribution of patients according to Comorbidity diagnosis, age and sex. The pattern shows a higher incidence of male subjects in heroin dependents sample (76% versus 24%) according to the literature [12]. The age distribution is homogeneous. Moreover our data report eighty percent of the total sample affected by a dual psychiatric diagnosis. Specifically the personality disorders are more represented in male group while mood disorders are prevalent in females, as has been found in other studies [13].

**Table 1. Descriptive socio-demographic characteristics data.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Addiction and no comorbidity</th>
<th>Addiction and anxiety disorder</th>
<th>Addiction and depression</th>
<th>Addiction and personality disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (±)</td>
<td>32.3 ± 6.0</td>
<td>34.7 ± 8.6</td>
<td>32.5 ± 6.7</td>
<td>31.9 ± 6.6</td>
</tr>
<tr>
<td>Gender(male/female)</td>
<td>26.6</td>
<td>10.4</td>
<td>22.16</td>
<td>65.13</td>
</tr>
<tr>
<td>Single</td>
<td>59.1%</td>
<td>62.5%</td>
<td>36.8%</td>
<td>60.97%</td>
</tr>
<tr>
<td>Married</td>
<td>27.3%</td>
<td>25%</td>
<td>42.1%</td>
<td>31.7%</td>
</tr>
<tr>
<td>Divorced/widower</td>
<td>13.6%</td>
<td>12.5%</td>
<td>21.05%</td>
<td>7.32%</td>
</tr>
<tr>
<td>Primary school</td>
<td>12.5%</td>
<td>0%</td>
<td>7.80%</td>
<td>10.28%</td>
</tr>
<tr>
<td>Secondary school</td>
<td>53.1%</td>
<td>50%</td>
<td>47.36%</td>
<td>52.56%</td>
</tr>
<tr>
<td>Diploma</td>
<td>31.2%</td>
<td>42.85%</td>
<td>39.47%</td>
<td>35.9%</td>
</tr>
<tr>
<td>University degree</td>
<td>3.1%</td>
<td>7.14%</td>
<td>5.26%</td>
<td>1.28%</td>
</tr>
<tr>
<td>Professional</td>
<td>25%</td>
<td>16.67%</td>
<td>16.67%</td>
<td>51.67%</td>
</tr>
<tr>
<td>Employee</td>
<td>4.55%</td>
<td>18.18%</td>
<td>40.91%</td>
<td>36.36%</td>
</tr>
<tr>
<td>Worker</td>
<td>23.08%</td>
<td>7.69%</td>
<td>10.26%</td>
<td>58.07%</td>
</tr>
<tr>
<td>Unemployed</td>
<td>21.35%</td>
<td>5.62%</td>
<td>25.84%</td>
<td>47.19%</td>
</tr>
</tbody>
</table>
Table 3 shows serum Mg++ levels in heroin dependent patients with and without psychiatric comorbidity. Mg++ levels were higher in patients with heroin dependence and personality disorders (2.01 ± 0.13) compared to heroinomans with depression (2.10 ± 0.15) and without comorbidity (2.08 ± 0.12). Patients with anxiety disorder comorbidity did not present significant differences (2.02 ± 0.08) as compared to patients without comorbidity. Besides, as shown in figure 1, male heroin dependent patients had lower Mg++ levels compared to females for all the four subgroups. This difference was not significant as a whole (2.05 ± 0.13 versus 2.03 ± 0.16), except in the subgroup without comorbidity (2.11 ± 0.09 versus 1.97 ± 0.19; p < 0.05).

Discussion
In this study we present data showing that serum Mg++ levels are lower in patients with both heroin dependence and personality disorders compared to heroin addicts with depression or without comorbidity and tend to be higher in males compared to females even though remaining in the normal range. Indeed, none of the patients included in the study suffered clinically relevant hyper- or hypomagnesemia. Actually, the subjects presented a fairly good health and nutritional status at medical assessment, and were treated with low dose methadone substitutive therapy. In contrast to Sadlik’s results [8], which demonstrated no difference between heroin dependent and normal controls in Mg++ levels, a recent study from Spanowska-Wolin et al. [14] showed

Table 2. Distribution of psychiatric co-diagnoses in the sample by sex and age.

<table>
<thead>
<tr>
<th>Comorbidity diagnosis</th>
<th>Male N: 123; Age: 33; 76%</th>
<th>Female N: 39; Age: 30; 24%</th>
<th>Total N: 162; Age: 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>No psychiatric comorbidity</td>
<td>N (Age)</td>
<td>%</td>
<td>N (Age)</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>26 (33)</td>
<td>21</td>
<td>6 (28)</td>
</tr>
<tr>
<td>Mood disorders</td>
<td>22 (33)</td>
<td>18</td>
<td>16 (32)</td>
</tr>
<tr>
<td>Personality disorders</td>
<td>65 (32)</td>
<td>53</td>
<td>13 (28)</td>
</tr>
</tbody>
</table>

Table 3. Serum magnesium levels per dual diagnosis (heroin addicts without comorbidity; heroin addicts with anxiety disorders; heroin addicts with depression; heroin addicts with personality disorders).

<table>
<thead>
<tr>
<th>Heroin addicts</th>
<th>Serum magnesium (mg/dL)</th>
<th>Serum magnesium (mg/dL)</th>
<th>Serum magnesium (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Total</td>
</tr>
<tr>
<td>Pt without comorbidity (A)</td>
<td>2.11 (0.09) 26</td>
<td>1.97 (0.19) 6</td>
<td>2.06 (0.12) 32</td>
</tr>
<tr>
<td>Anxiety disorders (B)</td>
<td>2.03 (0.09) 10</td>
<td>2.00 (0.00) 4</td>
<td>2.02 (0.08) 14</td>
</tr>
<tr>
<td>Depression (C)</td>
<td>2.11 (0.16) 22</td>
<td>2.10 (0.14) 16</td>
<td>2.10 (0.15) 38</td>
</tr>
<tr>
<td>Personality disorders (D)</td>
<td>2.01 (0.12) 65</td>
<td>1.98 (0.19) 13</td>
<td>2.01 (0.13) 78</td>
</tr>
<tr>
<td>Total</td>
<td>2.05 (0.13) 123</td>
<td>2.03 (0.16) 39</td>
<td>2.05 (0.14) 162</td>
</tr>
</tbody>
</table>

ANCOVAS dual diagnosis (Factorial: 4 levels)

Age like covariate

Dual diagnosis

F(3.118): 5.5**
F(3.34): 1.7
F(3.157): 5.4**

Significant LSD post hoc

A versus D**
C versus D**

*: p<0.05; **: p<0.01. Normal range serum magnesium: 1.80-2.40 mg/dL.
lower levels in drug addicts, related to lower mineral dietary intake than in controls: This difference disappeared after two months of methadone treatment. To date, systematic clinical data about Mg$^{++}$ levels in methadone treatments are not available: a study by Christensen et al. [15] showed, by MR spectroscopy, that free Mg$^{++}$ concentration is not related to methadone dose or to the number of days of abstinence in polydrug abusers. So, in our sample the methadone treatment should be an alternative explanation of overall magnesium levels in indirect way, as outlined by Spanowka-Wohn, as a result of a better nutritional status in methadone treated subjects.

Gender differences in our sample show the same direction as in studies about normal healthy subjects [13], showing higher serum Mg$^{++}$ values in males than in females. In these studies, a significant negative correlation was found between serum Mg$^{++}$ and both estrogen and progesterone peaks. This relation between magnesium levels and sex steroid hormones could cyclically contribute to lower magnesium levels in child-bearing age women [16]. Nevertheless, in our samples, a limit to the generalization of this result is the low number of women in the no-comorbid subgroup, where gender differences were significant. Moreover, the data collection method should be improved by control of the ovarian cycle phase in participant women.

On the whole, a psychiatric comorbidity effect appears more relevant than gender differences and than drug addiction diagnosis.

As regards to the effect of comorbidity depression, our results are congruent with previous studies, showing higher levels in depressed subjects than in healthy controls. Our results are also consistent with Imada’s observations [3] in affective disordered patients, with both higher Mg$^{++}$ in the whole depression subgroup and lack of significant gender differences.

The sign of difference in personality disordered addicts is opposite, and analogous to differences reported in schizophrenia. We hypothesize that this result is related to shared features between schizophrenia and personality disorders, especially borderline personality, such as dissociation and impulsiveness. Further studies are needed to clarify this analogy and to assess differences between each personality disorder.

**Conclusion**

In relation to drug addiction, few studies have investigated biological markers, which can be critical in the initiation of substance use or in the progression towards dependence [17].

Dual diagnosis significantly modifies magnesium levels in our drug dependent sample. Gender slightly modifies magnesium levels in non comorbid subjects, so that females show significantly lower magnesium levels compared to males. The presence of psychiatric comorbidity abates this difference.
In order to research their effects on ion channels and on signal transduction in neuroadaptation resulting from exposure to drugs of abuse, a multidisciplinary approach involving physiology, molecular biology, genetic engineering and behavioral analysis seems to be extremely important [18].

References