Plasma magnesium level and psychomotor retardation in major depressed patients

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Abstract. Numerous studies have been performed on magnesium (Mg) metabolism in patients with mood disorders but consistent results have not been obtained. To date, systematic clinical data about Mg levels in major depressed patients according to the psychopathological profile are not available. In the present study we have investigated the relationship between plasma Mg level severity of symptoms and specific psychopathological dimensions (anhedonia and retardation) in 53 mild-to-moderately depressed patients (M/F = 21/32; mean age 46.49 ± 13.48). The psychopathological status was assessed using standard psychometric evaluation scales: HAM-D for severity of depression, HAM-A for severity of anxiety symptoms, DRSS for psychomotor retardation and SHAPS for anhedonia. We did not find any significant correlation between total plasma Mg levels (0.86 ± 0.09 mmol/L), severity of depression (HAM-D = 17.13 ± 6.76) and anxiety (HAM-A = 16.62 ± 6.60). A statistically significant correlation between Mg levels and psychomotor retardation was observed. Patients with higher psychomotor retardation scores (DRRS = 20.41 ± 7.72) showed higher plasma Mg levels (0.89 ± 0.07 mmol/L), even though they remained in the normal range, in comparison to patients with lower retardation scores (DRRS = 7.29 ± 3.80; Mg = 0.82 ± 0.10 mmol/L). A relationship between catecholamines and Mg metabolism has been described and our results support the hypothesis that hypermagnesaemia might lead to hypoactivity and psychomotor retardation which is so often observed in depressed patients.

Key words: major depression, magnesium, psychomotor retardation

Magnesium (Mg) is an essential trace mineral that is involved as a coenzyme in numerous enzyme reactions in organisms. Because Mg also influences the nervous system via its actions on the release and metabolism of neurotransmitters and other mechanisms, abnormal Mg metabolism has been implicated in several neuropsychiatric disorders with prominent mood and physical symptoms (e.g., migraine, epilepsy, chronic pain) [1-4]. A relation between Mg and affective disorders has also been suggested since low cerebrospinal fluid levels of Mg have been observed in patients with suicidal behaviour [5]. On the other hand, a mood-improving efficacy of Mg has been observed in patients with chronic fatigue syndrome [6] or with premenstrual syndrome [7] and also in patients with features that might be related to atypical depression [8].

To date, numerous studies have been performed on Mg metabolism in patients with mood disorders but consistent results have not been obtained. Many studies have shown that serum/plasma Mg levels are higher in patients with mood disorders than in normal subjects [9-18]. On the other hand, Young et al. [19] failed to show any difference between the two groups, while some authors found lower Mg levels in patients with mood disorders [20-23].
Considerable interest has also been shown in the possible relationship between Mg levels and both the severity and the therapeutic course of the disorder. Widmer et al. [10, 16-18] reported that plasma and erythrocyte Mg levels were higher in patients with mood disorders than in normal subjects, both before and after treatment, and pointed out that this is a disease-specific manifestation. In addition, with regard to the relationship between the drugs used to treat mood disorders and Mg levels, it has been reported that lithium carbonate increases plasma/serum Mg levels [13, 24] and that determination of serum Mg$^{2+}$ and Ca$^{2+}$ levels is useful in predicting the antidepressive effect of lithium [25].

Furthermore, drug therapy using Mg has been attempted [26] and much interest has recently been shown in the relationship between the mechanisms of action of mood stabilizers and Mg metabolism. The influence of Mg on systems that might be involved in the pathophysiology of depression has also been reported. A direct impact of magnesium on the function of the transport protein p-glycoprotein at the level of the blood-brain barrier has been demonstrated, possibly influencing the access of corticosteroids to the brain [27, 28]. Moreover a stimulating effect on the Na/K-ATPase activity has also been reported, together with indirect effects, including antagonistic to N-methyl-D-aspartate and agonistic to GABA [28].

The main aim of the present study was to investigate the relationship between total plasma Mg levels and specific psychopathological dimensions (anhedonia and retardation) in patients with major depressive episode (MDE).

**Materials and methods**

The study was carried out from December 2006 through February 2007 and was approved by the local Ethical Committee. Among psychiatric patients consecutively admitted to the Institute of Psychiatry of the Catholic University in Rome, 53 patients (M/F = 21/32; mean age 46.49 ± 13.48) with Major Depressive Disorder (MDD) who met the Diagnostic and Statistical Manual (DSM-IV) criteria based on clinical interview, using a Structured Clinical Interview for DSM-IV, were randomly recruited. Patients who had a history of any concomitant psychiatric illness, such as substance abuse, alcohol or cigarette abuse, history of infections or known autoimmune diseases were excluded. Also excluded were those patients who were 10% above ideal body weight, suffered any endocrine, immune or metabolic disorder, inflammatory bowel disease or AIDS. Similarly subjects who suffered from an allergic reaction or inflammatory response in the previous two weeks were excluded from the study.

All subjects showed normal laboratory findings in blood chemistry, renal, thyroid, liver function and ECG and also were drug free for at least 2 weeks.

Laboratory testing for the assay of magnesium and psychopathological status were assessed at the same time in all depressed patients, upon admission, at the Day Hospital of the Psychiatric Institute of the Catholic University. The psychopathological status was assessed by the same trained physician, blind to diagnosis, using the Brief Psychiatric Rating Scale (BPRS) for the overall burden of psychopathology, 21-item Hamilton Depression rating Scale (HAM-D) [29] for depression, Hamilton Anxiety Rating Scale (HAM-A) [30] for anxiety, Snaith-Hamilton Pleasure Scale (SHAPS) [31] and Depression Retardation Rating Scale (DRRS) [32] for anhedonia and psychomotor retardation.

All subjects provided a 9 mL blood sample, collected in heparin tubes between 08.00 and 09.00 in the Day Hospital of the Institute of Psychiatry. The total plasma levels of magnesium were measured with a colorimetric assay using a reagent by Olympus. This system was able to detect concentrations of magnesium as low as 0.01 mmol/L, in a normal range between 0.75 and 1.08 mmol/L.

**Data analysis**

Data are expressed as the mean ± SD. In order to investigate correlations between Mg levels and psychopathological features, we used the median value of the measured variables to divide the population into subgroups. For comparison between subgroups, a one-way analysis of variance (ANOVA) was performed. The association between plasma magnesium levels and total scores of psychometric scales were tested for significance using the Pearson's chi-square test.

All calculations were performed using the STATA 6.0 statistical software package (Stata Corporation, College Station, TX) and the results were considered statistically significant when the p value was < 0.05.

**Results**

Table 1 shows the results of plasma Mg levels and the psychometric evaluation of our sample. Patients could be considered mild-to-moderately depressed and also showed a specific psychopathological profile with relevant psychomotor retardation and/or
significant anhedonic features. None of the patients included in the study suffered clinically relevant hyper- or hypomagnesaemia and the majority of the patients showed magnesium levels in the normal range.

In order to investigate correlations between Mg levels and psychopathological features, we used the median value to stratify the population into two subgroups: (a) “higher Mg levels” (Mg > 0.83 mmol/L), and (b) “lower Mg levels” (Mg < 0.83 mmol/L). These two subgroups showed a statistically significant difference (0.92 ± 0.05 mmol/L versus 0.80 ± 0.08 mmol/L; F = 35.514, p < 0.0001).

We did not observe any significant correlation with severity of depression and anxiety symptoms (Table 2). In addition, we compared the psychopathological profile of the two subgroups and a statistically significant correlation between plasma Mg levels and psychomotor retardation (total score on DRRS) was observed (Table 2). Patients with higher (DRRS > 11) psychomotor retardation scores (DRRS total score = 20.41 ± 7.72) showed a statistically significant correlation with normal range of total plasma magnesium = 0.75-1.08 mmol/L.

Table 1. Descriptive psychometric evaluation and total plasma magnesium data.

<table>
<thead>
<tr>
<th>N Valid</th>
<th>HAM-D Total Mean</th>
<th>HAM-A Total Median</th>
<th>BPRS Total Median</th>
<th>DRRS Total Median</th>
<th>SHAPS Total Median</th>
<th>Total Mg (mmol/L) Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>53</td>
<td>17.13</td>
<td>16.62</td>
<td>33.29</td>
<td>13.51</td>
<td>2.89</td>
<td>0.86</td>
</tr>
<tr>
<td>Mean</td>
<td>18</td>
<td>18</td>
<td>32</td>
<td>11</td>
<td>2</td>
<td>0.83</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>6.76</td>
<td>6.60</td>
<td>6.45</td>
<td>8.80</td>
<td>3.47</td>
<td>0.09</td>
</tr>
</tbody>
</table>

In clinical practice depressed and anxious patients frequently show a total scores > 15 at HAM-D and HAM-A (> 18 in moderate to severe conditions). BPRS scores > 39 are typically observed in psychiatric patients who require hospitalization. DRRS scores > 10 can be observed in depressed patients with clinically significant psychomotor retardation (>18 in more severe conditions). SHAPS scores > 4 are reported in anhedonic patients (> 7 in more severe conditions).

Table 2. The distribution of patients according to magnesium levels and psychopathological features. Patients were divided into subgroups, using the median values of the measured variables.

| Total Plasma Mg Levels | Total | “Lower” (Mg < 0.83 mmol/L) | “Higher” (Mg > 0.83 mmol/L) | Pearson Chi-square | p  
<table>
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<tr>
<td>HAM-D Total Score</td>
<td></td>
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<tr>
<td>“Lower” (&lt; 18)</td>
<td>20</td>
<td>9 (45.0%)</td>
<td>11 (55.0%)</td>
<td>0.833</td>
<td>0.361</td>
</tr>
<tr>
<td>“Higher” (&gt; 18)</td>
<td>31</td>
<td>18 (58.1%)</td>
<td>13 (41.9%)</td>
<td></td>
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<tr>
<td>HAM-A Total Score</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>“Lower” (&lt; 18)</td>
<td>28</td>
<td>16 (57.1%)</td>
<td>12 (42.9%)</td>
<td>0.689</td>
<td>0.406</td>
</tr>
<tr>
<td>“Higher” (&gt; 18)</td>
<td>20</td>
<td>9 (45.0%)</td>
<td>11 (55.0%)</td>
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<td></td>
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<tr>
<td>BPRS Total Score</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>“Lower” (&lt; 32)</td>
<td>29</td>
<td>17 (58.6%)</td>
<td>12 (41.4%)</td>
<td>0.882</td>
<td>0.348</td>
</tr>
<tr>
<td>“Higher” (&gt; 32)</td>
<td>20</td>
<td>9 (45.0%)</td>
<td>11 (55.0%)</td>
<td></td>
<td></td>
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<tr>
<td>DRRS Total Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Lower” (&lt; 11)</td>
<td>23</td>
<td>15 (65.2%)</td>
<td>8 (34.8%)</td>
<td>4.464</td>
<td>0.035</td>
</tr>
<tr>
<td>“Higher” (&gt; 11)</td>
<td>21</td>
<td>7 (33.3%)</td>
<td>14 (66.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHAPS Total Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Lower” (&lt; 2)</td>
<td>19</td>
<td>9 (47.4%)</td>
<td>10 (52.6%)</td>
<td>0.046</td>
<td>0.830</td>
</tr>
<tr>
<td>“Higher” (&gt; 2)</td>
<td>16</td>
<td>7 (43.7%)</td>
<td>9 (56.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Psychopathological assessment was performed using standard psychometric evaluation scales: HAM-D for severity of depression, HAM-A for severity of anxiety symptoms, BPRS for the overall burden of psychopathology, DRRS for psychomotor retardation and SHAPS for anhedonia.

* The association between plasma Mg levels and psychometric scores was tested for significance using the Pearson’s chi-square test.
also showed higher plasma Mg levels (0.89 ± 0.07 mmol/L) in comparison to patients with lower (DRRS < 11) retardation scores (DRRS total score = 7.29 ± 3.80; Mg = 0.82 ± 0.10 mmol/L).

Discussion

In a previous study on heroin addicts, we observed higher serum Mg levels in a sample of patients with both heroin dependence and depression, compared to heroin addicts with personality disorders [33]. No consensus has been achieved about Mg in mood disorders. Most of the studies concerned patients under treatment and there is often a lack of information about the distribution of the sample in clinical subgroups, type of treatment and severity of illness. To date, systematic clinical data about Mg levels in major depressed patients according the psychopathological profile are not available.

In this study we present data showing that in drug-free major depressed patients with relevant psychomotor retardation compared to patients with lower retardation, total plasma Mg levels are higher even though remaining in the normal range.

Since the observations of the earliest psychiatric writers, including Aretaeus of Cappadocia, Hippocrates, Caelius Aurelianus and Plutarch, psychomotor disturbances continue to be regarded as an essential feature of major depressive disorder. Objectively measured motor behaviour, including gross motor activity, discrete body movements, speech, and motor reaction time, have been shown to reliably differentiate depressed patients from psychiatric and normal comparison groups [34].

Historically, psychomotor symptoms contributed significantly to the evolving nosology of depression subtypes. Some studies sought to isolate the clinical differences between psychotic and neurotic patients, and it was repeatedly found that delusions and psychomotor symptoms were the most robust subtype discriminators for the most severe conditions [35]. In addition, psychomotor disturbance can be considered one of the objectively measurable features of endogenous depression that has long been recognized as associated to central catecholaminergic deficiency [30].

A relationship between catecholamines and Mg metabolism has been described and an overactivity of peripheral catecholamines associated with blood hypomagnesaemia has been reported [37]. A low Mg/Ca ratio has also been associated to an increased release of catecholamines, which lowers tissue Mg levels [38].

Widmer et al. [10] hypothesized that, if central and/or peripheral Mg deficiency seems to promote active behaviour and, therefore, increases catecholamine output, hypermagnesaemia might lead to the hypoactivity and psychomotor retardation so often observed in depressed patients. Our results are in good agreement with this hypothesis, for the reason that, in our sample, patients with higher psychomotor retardation scores also showed significantly higher plasma Mg levels.

In the literature, some interest has been shown in the possible relationship between Mg levels and both the severity and the therapeutic course of depressive disorders. Widmer et al. [10] observed that medium and severely depressed patients had much higher erythrocyte Mg levels than slightly depressed patients. They suggest a relation between Mg levels and the severity of depression. In contrast, in our sample we failed to report any correlation between the severity of psychopathology (total score on HAM-D and BPRS) and Mg levels.

Some methodological limitations are present. First of all, the number of recruited patients is limited. Biological data are incomplete and there is a lack of information about ionized magnesium or intra-erythrocyte magnesium (ery-Mg). Acute physical or psychological stress, differences in physical health, activity and arousal levels may have influenced the results in a non-predictable way.

Conclusion

Very few studies have analyzed Mg levels in depressed patients according to the clinical features. In our sample psychomotor retardation significantly correlated with total plasma Mg levels. These results support the hypothesis that Mg metabolism might to be linked to active behaviours and catecholaminergic activity [10]. A multidisciplinary approach and further research in larger samples are needed to clarify the involvement of Mg in major depression and its relation to brain aminergic systems.

References

MAJOR DEPRESSION AND PLASMA MAGNESIUM


