UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA
FACULTY OF MEDICINE

CLINICAL, EVOLUTIVE AND THERAPEUTICS
CORRELATIONS IN SCHIZOPHRENIA

Ph.D.THESIS
- ABSTRACT-

SCIENTIFIC SUPERVISOR :
Professor M.D. Ph.D.
DRAGOŞ MARINESCU

Ph.D. STUDENT
EMILIA BURADA (RĂDUCANU)

CRAIOVA 2010
INTRODUCTION

Schizophrenia is a very important health problem and it affects almost 1 % of world population. The etiology and pathology of schizophrenia are topics of many studies and many theories were formulated in order to explain them. A new generation of drugs and the most recent discoveries concerning the pathology and the genetic factors, lead to a new view on schizophrenia, but with all these it remains a mysterious disease with a great impact on patients and their families.

The schizophrenia treatment was and still is a permanent challenge for the physicians, almost all the patients benefit by antipsychotic medication. The antipsychotic drugs can be divided into two categories: the old generation (dopamine antagonist) and the new generation (the serotonin-dopamine antagonist). Noncompliance at antipsychotic treatment is quite high.

Keywords: schizophrenia, neurodegeneration, antipsychotic drugs, extrapyramidal effects, homocysteine, vitamin B12.
One of the noncompliance cause is the presence of extrapyramidal effects (EPS). The most important extrapyramidal effects are: akathisia, parkinsonism, dystonia, dyskinesia, tasykinesia, Pisa syndrome, tardive dystonia, tardive tics, and so on.

The prevention, treatment and identification of prediction factors for extrapyramidal effects appearance and severity has an important significance. Although, the variable response to treatment, the presence of extrapyramidal effects at patients treated with atypic antipsychotics that block less the dopamine receptors and more the serotonine receptors, prove the fact that there are other factors that influence the evolution of the disease.

One of these factors can be the elevated levels of homocysteine. The level of homocysteine can be considered a risk factor for a variety of central nervous system diseases including Alzheimer disease, schizophrenia, cognitive impairment in the elderly, neuroleptic-induced tardive movement disorders, including tardive parkinsonism and tardive dyskinesia, other movement disorders such as idiopathic Parkinson's disease, Huntington's disease and primary dystonia. Recent studies showed a negative correlation between levels of folate, vitamin B12 and negative symptoms of schizophrenia and a positive correlation between the levels of homocysteine extrapyramidal effects and cognitive disturbance. Also a high level of homocysteine is correlated with the degree of brain atrophy at patients with schizophrenia.

II. SPECIAL PART – PERSONAL CONTRIBUTIONS

Chapter V. Motivation and Objectives

The purpose of this study was:
- to emphasize and to evaluate the extrapyramidal effects of antipsychotic drugs at schizophrenic patients,
- to establish correlations between type and duration of treatment and the presence of extrapyramidal effects,
- the analysis of some biologic markers linked with extrapyramidal effects, that might be indicators of disease evolution and prognostic.

Chapter VI. Materials and Method

In this study there were included schizophrenic patients from LSM Craiova, between 1996-2005. The work protocol includes the following parts:
- Establish criteria for including the patients
•Gathering the anamnestic dates, about the personal and pathological antecedents the way and age of onset ( the period between the first symptoms and the moment of diagnosis ant the initiation of therapy), the therapy before this ( tipic antipsychotic or/and atipic antipsychotic).

•The patients neurologic exam with focus on evaluation of extrapyramidal effects and applying scales: ESRS (extrapyramidal symptom rating scale) and Simpson-Angus Rating Scale. After that the patients were divided into three categories: i) minimal EPS+, ii) medium EPS+, iii) severe EPS+.

• The psychiatric exam with focus on cognitive evaluation (scale MMSE), and applying PANSS (Positive and Negative Syndrome Scale). The patients were divided in three categories: i) without cognitive impairment; ii) with minor cognitive impairment; iii) with severe cognitive impairment.

•Estimate the patients evolution and divided them in three categories: i) good evolution, ii) medium evolution; iii) bad evolution.

•Grading the biological markers:
  - homocysteine, vitamin B12, folic acid at patients with severe EPS
  - prolactine at patients with severe cognitive impairment.

•Imagining evaluation with cerebral CT scan at patients with severe cognitive impairment and severe extrapyramidal effects.

•Biostatistic analysis (standard deviation, t –Student test, Mann–Whitney test, CHI-square test).

Chapter VII. Results

The catamnestic study. In this study were included 200 patients diagnosed with schizophrenia (107 women and 93 men). The patients were aleatory chosen and were between 18 and 60 years old with the average 38.8± 4.66 (for women 40.36±4.31 and for men 37.33 ±6.12 years).

The inclusion criteria: a) patients age between 18 and 60 years b) patients diagnosed with schizophrenia according to DSM IV, c) at least 10 years evolution, d) in LSM Craiova evidence from 1996, e) treated with antipsychotics typical and/or atypical

The exclusion criteria: a) the existance of other psychiatric diseases, b) patients with cerebral trauma, c) elements of another organic disease, d) catatonic type of schizophrenia.

From these patients 51% were diagnosis with undifferentiated subtype, 36% were paranoid subtype, 12% were with affective schizophrenia and just 1% with residual subtype. The patients evolution in this period was the following one: 27 patients had a good evolution (13,5%), 55 patients had medium evolution (27,5%) and 118 had bad evolution (59%) (the evolution was established using a group of criteria). All the patients with good evolution had in their treatment new generation
antipsychotics, the patients with bad evolution were treated with typical antipsychotics +/- atypical (table 1).

**Table 1. Patients distribution according to evolution and treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AP I</th>
<th>API/APIII</th>
<th>AP II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good evolution</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>27 (13.5%)</td>
</tr>
<tr>
<td>Medium evolution</td>
<td>2 (1%)</td>
<td>31 (15.5%)</td>
<td>22 (11%)</td>
</tr>
<tr>
<td>Bad evolution</td>
<td>46 (23%)</td>
<td>65 (32.5%)</td>
<td>7 (3.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>48 (24%)</td>
<td>96 (48%)</td>
<td>56 (28%)</td>
</tr>
</tbody>
</table>

From 200 patients, 106 (53%) presented extrapyramidal effects, all these patients being included in the group with bad evolution. Extrapyramidal effects appeared at different times, the most frequent appeared immediately (52.9%), in 6 months (21.7%), in first year (4.7%), in second year (14.1%) in the third year (3.8%), after 3 years (2.8%). Most cases with extrapyramidal effects appeared after typical antipsychotic treatment (38 patients), and, at patients that had in their antecedents treatment with typical antipsychotics, even if now they are treated with atypical antipsychotics (63 cases). Only 5 patients with EPS had only atypical antipsychotics (table 2).

**Table 2. Patients distribution according to treatment and EPS**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AP I</th>
<th>API/APIII</th>
<th>AP II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapyramidal effects +</td>
<td>38 (19%)</td>
<td>63 (31.5%)</td>
<td>5 (2.5%)</td>
</tr>
<tr>
<td>Extrapyramidal effects -</td>
<td>10 (5%)</td>
<td>33 (16.5%)</td>
<td>51 (25.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>48 (24%)</td>
<td>96 (48%)</td>
<td>56 (28%)</td>
</tr>
</tbody>
</table>

To establish a correlations between treatment and extrapyramidal effects, I applied Chi-square test. The analysis results showed a strong association between typical antipsychotics and the presence of extrapyramidal effects (table 3).

**Table 3. Statistic correlation between EPS and treatment**

<table>
<thead>
<tr>
<th>Table of Chi-square by cell:</th>
<th>AP I</th>
<th>API/APIII</th>
<th>AP II</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPS +</td>
<td>(+) ***</td>
<td>(+) ***</td>
<td>(-) ***</td>
</tr>
<tr>
<td>EPS -</td>
<td>(-) ***</td>
<td>(-) ***</td>
<td>(+) ***</td>
</tr>
</tbody>
</table>

***: Chi-square by cell test significant at the level of significance alpha=0.010
Clinical evaluation

After neurological exam we divided the patients with EPS in three categories: 1) patients with minimal EPS + (54 cases - 50,94%); 2) patients with medium EPS + (33 cases - 31,13%); 3) patients with severe EPS + (19 cases -17,93%).

The most frequent EPS was the parkinsonism followed by oro-facial dyskinezia, dystonia and akathisia. The patients distribution was 70,76 % parkinsonism, 24,53% dyskinezia, 2,83% dystonia, 1,87 % akathisia. The patients distribution according the EPS type and its severity is the next one: i) severe EPS+: 13 patients with parkinsonism, 4 with dyskinezia, 1 with dystonia, 1 with akathisia; ii) medium EPS +: 21 with parkinsonism, 13 with dyskinezia, 2 with dystonia, 1 with akathisia; iii) minimal EPS +: 41 with parkinsonism, 13 with dyskinezia, no one with dystonia or akathisia.

Biological evaluation

We dosed homocysteine, vitamin B12, folate at patients with severe EPS.

**Homocysteine dosage:** (normal value: 5-12 micro mol/l). Patients distribution according to homocysteine value was:
- 3 patients had high homocysteine (13,9- 24,8 µmol/L) – 16%
- 4 patients had blood homocysteine higher than 10 µmol/L – 21%
- 12 patients had normal values - 63%

Patients distribution according to homocysteine level and type of extrapiramidal effects was: 3 pacients with parkinsonism and high level of homocysteine, 4 patients with levels higher than 10 µmol/L (1 with dyskinezia, 1 with dystonia, 2 with parkinsonism), and normal levels 12 patients (8 with parkinsonism, 1 with akathisia and 3 with dyskinezia).

To establish statistic a correlation between extrapyramidal effects and homocysteine level we applied Mann Whitney test and the test did not show a semnificative correlation between extrapyramidal effects and homocysteine p= 0,199 (p>0,05). But if we take into consideration the patients with homocysteine higher than 10 µmol/L, a higher procent of patients had modified homocysteine (37%).

**Vitamin B12 dosage:** normal values: 197 – 866 pg/mL. Patients distribution according to vitamin B12 level was:
- 5 patients had low levels (76.39 pg/mL - 200 pg/mL) - 26 %
- 2 patients had levels lower than 250 pg/ml– 11%
- 12 patients had normal levels – 63%
Biostatic analysis using Mann Whitney test showed an association between extrapyramidal effects and vitamin B12 levels p= 0.017 (p<0.05). Also there is a correlation between increased homocysteine levels and decreased vitamin B12 levels (figure 1).

![Figure 1. Correlation between homocysteine levels and vitamin B12](image)

**Folate dosage**: normal values: 3.1 – 17.5 ng/mL. Blood folate distribution at patients with extrapyramidal effects was: 4 (22.22%) patients had normal levels, but very close to lower level (3.3 – 3.8 ng/mL) and 14 patients had normal levels (77.78%). Biostatistic analysis did not showed an association between extrapyramidal effects and folate levels p=0.367 (p>0.05)- Mann Whitney test.

**Prolactine dosage**: normal values: 127 - 637 µUI/mL. High levels of prolactine were revealed at 60% of patients, from these 3 patients had very high levels (more than 1000 µUI/mL) from patients with severe cognitive impairment.

**Imagistic evaluation**. The following abnormalities were observed after cerebral CT: cerebral atrophy (especially frontal lobes), cerebelous atrophy, ventriculomegaly. The following images are selected from the cerebral exam of an paranoid schizophrenia patient, treated with atypical antipsychotics, with extrapyramidal effects (parkinsonism) and homocysteine level high (24.8 µmol/L), vitamin B12 level: 76.39 pg/mL and blood folate: 7.6 ng/mL (figure 2).

![Figure 2. Cerebral CT scan: cerebral atrophy, ventriculomegaly](image)
CONCLUSIONS

• Extrapyramidal effects are an important problem at patients treated with antipsychotics, being a clinical indicator associated with an unfavorable evolution. The study results showed that most patients with extrapyramidal effects were treated with typical antipsychotics (35.84%) or had in their past typical antipsychotics in treatment (59.43%) and only a small percentage were treated with typical antipsychotics (4.71%).

• Patients evolution in this period was: good at 27 patients (13.5%), medium at 55 patients (27.5%) and bad evolution at 118 patients (59%). Data analysis showed a strong association between atypical antipsychotics and good evolution and typical antipsychotics and bad evolution (p < 0.0001).

• Extrapyramidal effects appeared after variable period of time: most frequent shortly, in the first month - 52.9%, at 21.7% in the first 6 months, at 4.7% in the first year, at 14.1% in the second year, at 3.8% in the third year and 2.8% after 3 years.

• The most frequent extrapyramidal effect was parkinsonism at 70.76%; at 24.53% appeared dyskinezia, at 2.83% dystonia and at 1.88% akathisia.

• Homocysteine levels distribution at patients with severe EPS showed high levels at 16% of patients. Even if the statistical analysis did not showed a semnificative correlation between extrapyramidal effects and homocysteine level (p= 0.199), if we take into consideration the patients with homocysteine level close to the higher limit, a semnificative percentage of patients (37%) with extrapyramidal effects had the homocysteine value abnormal.

• Hyperhomocysteine has an important role in some neuropsychiatric diseases pathology and it may be considered a neurodegeneration biomarker. Neurodegeneration acceleration through higher neuronal excitotoxicity NMDAmediated and oxidative stress caused by hyperhomocysteine may be involved in schizophrenia pathology.

• Vitamin B12 levels distribution at patients with severe EPS showed that 27% of patients had low levels of homocysteine and 11% had levels close to the inferior limit (< 250 pg/ml). Biostatistic analysis reveled an association between extrapyramidal effects and vitamin B12 low level p= 0.017 (p<0,05)- Mann Whitney test. Also their is a correlation between vitamin B12 decreases and homocysteine increases.

• Biostatistical analysis did not showed any association between folate level and extrapyramidal effects p=0,367 (p>0,05)-Mann Whitney test.
• Prolactine distribution levels showed high levels at 60% of patients with severe cognitive impairment.
• Imagistic evaluation showed abnormalities: cerebral and cerebelous atrophy, ventriculomegaly.
• One of noncompliance`s reasons is the extrapyramidal effects presence. Taking into consideration the extrapyramidal effects invalidant feature is ones more underlined the importance of their prevention, treatment and restriction and also the importance to identify indicators of their severity.

**CURRICULUM VITAE**

**NAME: EMILIA BURADA (RADUCANU)**

Birth date: February 4, 1980

**STUDY:**
1998-2004: Medicine Faculty from University of Medicine and Pharmacy Craiova,

**POSITIONS AND PROFESSIONAL TRAINING:**
- 2005-2006, neurology resident, Emergency Hospital Târgu Mures
- 2006-2009, neurology resident, Emergency Hospital, Craiova,
- 2009-present, neurologist
- 2004-present, PhD student at University of Medicine and Pharmacy Craiova, in the field of Psychiatry.

**GRANT**
Project manager - Clinical, evolutive and therapeutics correlations in schizophrenia (2008 -2010), grant CNCSIS type TD 2008, code CNCSIS 144, contract number 133/15.09.2008 (financial support for this research)

**PUBLICATIONS:**

I. Articles
- Elena Buteica, Aurelia Enescu, **Emilia Burada** – Clinical and cytogenetic study of some cases with psychomotor abnormalities, Moderne Medicine, vol. XIV, no. 12, 657-660, 2007
- Zorica-Ileana Hertzog, R. Hertzog, Amelia Dobrescu, F.Burada, V.Mixich, **Emilia Burada**. Numerical and structural chromosomal changes in a case of autism, Romanian Biotechnological Letters vol. 12, (3) 3269-3275, 2007 [ISI]

**II. Abstracts published at scientific meetings**


**INTERNATIONAL FELLOWSHIP:**

- EFNS Department – Department Programme, Germany 2010
- International Teaching Course *Current treatments in neurology*, Milan, Italy, 20-24.06. 2009;
- The EFNS Academy for Young Neurologists, Prague May 15 – 18, 2008

**COURSES:**

- Cerebral ultrasonography Course, Bucharest, 6-27.02.2009
- International Regional Teaching Course in Neurology, Sovata, Romania, 2007,
- International Regional Teaching Course in Neurology, Bucharest, Romania, 2006
- Asistence in Alzheimer disease, Craiova 28.09. 2006
- Dopaminergic continuu stimulation in Parkinson disease, May 2006, Bucharest
- New therapeutic aspects in dementia, May 2006 Bucharest
- New Pharmaceutical formulas in therapeutics, May 2006, Bucharest
- Diagnosis and treatment problems in dementia 31.01-05.02 2005, Craiova, Romania.
- News in schizophrenia treatment 14.02-18.02 2005, Craiova Romania.