β2-microglobulin: a biomarker for bipolar disorder and schizophrenia?

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Context

Bipolar disorder (BD) and schizophrenia (SZ) are staging disorders1,2:

- Progressive cognitive decline / global functioning worsening,
- Persistence during remitting phases.

Immuno-inflammatory dysfunction hypothesis: field of immunopsychiatry:

- "Brain-on-fire" / neuroinflammation during acute episodes,
- Need for immune dysfunction biomarkers.

β2-microglobulin (β2M) = possible candidate for cognitive decline in BD/SZ:

- Part of major histocompatibility complex class I (MHC-I) on cells (Fig.A),
- Soluble circulating isoform level reflects cellular immune system activation3,4,
- Pivotal role of MHC-I in neuro-development/plasticity, recent data on β2M in ageing processes and cognitive deterioration5,6 (Fig.B).

Relationship between serum β2M circulating level and psychiatric condition onset and evolution remain to be studied6. Hypothesis: serum β2M level may reflect acute episodes and severe functioning impairment in bipolar disorder and schizophrenia.

Methods

Preliminary analysis: β2M levels from an ongoing multi-centric cohort:

- 104 BD / 37 SZ inpatients on acute episode,
- Assessed twice: after admission / before discharge within 3 months,
- 28 BD / 26 SZ outpatients on stabilized phase,
- 69 healthy controls.

Clinical assessment by standardized psychiatric interview, including:

- MADRS, YMRS, PANSS for specific symptom dimensions,
- GAF, CGI, FAST to evaluate global functioning.

Data analysis using R statistical software (CRAN) on β2M levels:

- Global ANOVA, then comparison between groups:
  - Acute vs stabilized / acute vs controls in each disorder by Welch t-test,
  - Acute episode admission vs discharge (test re-test) by paired t-test,
  - Linear regression with specific symptom dimensions and global functioning:
    - Univariate on total scores from clinical scales,
    - Multivariate on dimensional scores including 5-factor PANSS model3,
  - Linear regression with age in specific groups.

Results

Significant β2M levels differences between groups: ANOVA p=1.3*10^-4,

- Group-by-group comparisons are detailed in Fig.1,
- Remained stable in test re-test comparisons on BD (p=0.60) and SZ (p=0.39) acute episodes.

No significant β2M levels correlations with clinical scales scores (p=0.05).

Significant β2M levels correlation with 5-factor PANSS sub-scores (Table 1):

- Good multivariated correlation in acute SZ episode (adjusted R²=0.45),
- Positive correlation with disorganization sub-score,
- Negative correlation with positive symptoms sub-score.

β2M levels correlation with age depends on diagnosis (Fig.2 / Table 2):

- Significant in BD and SZ: around 0.017 μg/mL elevation per year,
- Regression slope shows tendency to be higher in BD (p=0.072) vs controls.

Conclusion

Our data suggest serum β2M level as:

- A state biomarker in bipolar disorder:
  - 1.5-1.6 μg/mL in healthy or euthymic subjects,
  - 1.9-2.0 μg/mL in manic or depressed bipolar patients;
- An illness and severity biomarker in schizophrenia:
  - Independent of the state (acute or stabilized),
  - Correlated with PANSS disorganization sub-score, i.e. cognitive impairment dimension;

- A biomarker with elevated inertia:
  - As it remains high within our 3-month window, even on remission.

Further exploration needed:

- Larger cohorts, to rise statistical power,
- Multiple mechanisms may play a role in brain-immune communication.

Table 1: Significant correlations between serum β2M levels and clinical symptomatology in acute SZ and BD.

<table>
<thead>
<tr>
<th>Factor</th>
<th>PANSS items</th>
<th>Slope ± SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline β2M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>N4+N7+G1+P4+G12</td>
<td>-0.10 ± 0.03</td>
<td>1.2*10^-3</td>
</tr>
<tr>
<td>Negative</td>
<td>G2+N3+G7+P5+G12</td>
<td>0.06 ± 0.03</td>
<td>0.036</td>
</tr>
<tr>
<td>Disorganization</td>
<td>N11+G12+P14+G20+P5</td>
<td>0.14 ± 0.04</td>
<td>1.1*10^-3</td>
</tr>
<tr>
<td>Excitement</td>
<td>G14+P4+P7+G8</td>
<td>-0.04 ± 0.04</td>
<td>0.34</td>
</tr>
<tr>
<td>Emotional distress</td>
<td>G2+G6+G13+G4</td>
<td>0.05 ± 0.04</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Table 2: Linear regression with age and diagnosis group.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age-coefficients ± SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar disorder</td>
<td>0.0179 ± 0.0043</td>
<td>5.8*10^-3</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>0.0168 ± 0.0076</td>
<td>0.032</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>0.0041 ± 0.0043</td>
<td>0.34</td>
</tr>
</tbody>
</table>

No conflict of interest to disclose

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