Background

- Microbial translocation from the gastrointestinal tract is associated with persistent inflammation, and might play a role in the pathogenesis of neurocognitive dysfunction during HIV-infection.
- (1→3)-β-D-Glucan (BDG) is a polysaccharide component of most fungal cell walls including Candida spp. In the absence of an active fungal infection, increased blood BDG levels may be an indicator of gut mucosal barrier disruption and microbial translocation.

Objective

To evaluate whether higher blood BDG levels correlate with impaired neurocognitive functioning in a cohort of HIV-infected adults on suppressive antiretroviral therapy (ART).

Methods

- **Study Design:** Cross-sectional cohort study
- **Participants and Samples:** Paired plasma and cerebrospinal fluid (CSF) samples were obtained from 21 adults with acute/early HIV diagnosis, early treatment and suppressed levels of HIV RNA in blood plasma throughout treatment.
  - Study samples were collected as part of a prospective study between December 2013 and June 2014 at UCSD.
  - 19 plasma and 16 CSF samples were stored at -80°C on the day of collection.
- **Neurocognitive assessment:** Neurocognitive functioning was evaluated by assessing global deficit score (GDS, >0.5 is considered at least mild cognitive impairment).
- **Data generated:** Plasma and CSF samples were tested for BDG, soluble CD14 (sCD14), and Interleukin-8 (IL-8), and correlation with GDS was assessed by assessing global deficit score (GDS, >0.5 is considered at least mild cognitive impairment).
- **Correlation between plasma BDG and IL-8 (r=0.12, n.s.) and plasma BDG and plasma sCD14 (r=0.38, n.s.).** The combination of all three biomarkers (BDG * IL-8 * sCD14) had the highest correlation with GDS (Spearman r=0.71; p<0.01, Table 1).
- Two CSF samples presented elevated BDG levels (45 and 53 pg/mL; Figure 1B), while all other samples had BDG levels < 10 pg/mL. Interestingly, these two samples originated from the two subjects with the highest GDS scores of the cohort.

Results

- Median GDS was 0.39 (range 0 - 2.67; 10 participants had GDS >0.5). Median plasma BDG level was 66 pg/mL (range: 20-101 pg/mL), median CSF BDG level was 5 pg/mL (range: 0-53 pg/mL).
- Higher levels of plasma BDG were associated with more severe cognitive impairment as measured by the GDS (Spearman r=0.47; p=0.04, Figure 1A).
- Correlation of other markers with GDS scores were as follows: IL-8 (r=0.55; p=0.014), sCD14 (r=0.4, n.s.), nadir CD4 count (r=0.01, n.s.). We found no significant correlation between plasma BDG and IL-8 (r=0.12, n.s.) and plasma BDG and plasma sCD14 (r=0.38, n.s.).
- The combination of all three biomarkers (BDG * IL-8 * sCD14) had the highest correlation with GDS (Spearman r=0.71; p<0.01, Table 1).

**Table 1: Plasma biomarkers and correlations with GDS**

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Results (median [IQR] or mean ± SD)</th>
<th>Spearman correlation with GDS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma BDG (pg/mL)</td>
<td>66 (36-76)</td>
<td>r = 0.47</td>
<td>0.04</td>
</tr>
<tr>
<td>IL-8 (pg/mL)</td>
<td>2.54 (1.72-4.25)</td>
<td>r = 0.55</td>
<td>0.01</td>
</tr>
<tr>
<td>sCD14 (ng/mL)</td>
<td>1194 (1065-1379)</td>
<td>r = 0.40</td>
<td>n.s.</td>
</tr>
<tr>
<td>BDG x IL-8</td>
<td>156 (73-263)</td>
<td>r = 0.57</td>
<td>0.01</td>
</tr>
<tr>
<td>BDG x sCD14 / 100</td>
<td>672 (383-1123)</td>
<td>r = 0.58</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IL-8 x sCD14 / 10</td>
<td>339 (191-513)</td>
<td>r = 0.52</td>
<td>0.02</td>
</tr>
<tr>
<td>BDG x sCD14 x BDG / 100</td>
<td>1818 (845-4253)</td>
<td>r = 0.71</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Figure 1: Correlation of blood BDG levels (A) and CSF BDG (B) with GDS**

Conclusions

- BDG may be an indicator of gut mucosal barrier disruption and a promising independent biomarker associated with neurocognitive functioning in virologically suppressed HIV infected individuals with high CD4 counts.
- In particular when BDG is combined with established markers of immune activation, diagnostic potential for neurocognitive functioning may be promising.

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