Neuropsychological assessment in HIV/AIDS and its challenges in Galati County

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Background

• HAND persists despite ARV (~50%).
• Neuropathology in HAART era:
  • less neuronal loss;
  • gliosis, microglial activation;
  • *abnormal protein deposition in brain* increased (immune activation, aging);
  • *synapto-dendritic damage persists.*
• The phenotype of HAND changed:
  • less opportunistic diseases;
  • less severe dementia with marked motor signs;
  • more milder cognitive disturbances;
  • increasing co-morbid conditions: age related metabolic changes, hypertension, mitochondrial aging, substance abuse, viral co-infections [HCV], toxicity of ARVs.
Objectives

➢ To calculate the NCD rate on HIV patients from Galati County by screening tests
➢ To compare the dynamic of NCD by screening tests on pediatric and adult epidemic groups
➢ To correlate the results of screening tests
Material and Methods

• Prospective study
• HIV/AIDS patients recorded in Galati Clinic
• Screening tests applied in 2 steps: 2010/11; 2013/14
  ➢ 3Q test (Simioni)
  ➢ iHDS: 4 items (Max 12 p)
  ➢ Depression Beck inventory (borderline 13)
• Interview based on open question & medical history to identify
  o neurocognitive confounding factors
    ➢ Severe psychiatric conditions
    ➢ Sequelae from previous CNS-OIs or other neurological diseases
    ➢ Cranial trauma
    ➢ Abuse of psychotropic drugs
    ➢ Alcohol abuse
  o Co-morbid conditions: HTA, diabetes, dyslipidemia, anemia, hipo-vitamin D
• ART CNS-effectiveness scores (Letendre S, 2010).
Neurocognitive Impairment: Diagnosis and Management

Algorithm for diagnosis and management of HIV-associated Neurocognitive Impairment (NCI)

All patients without highly confounding conditions (i)

Screening for NCI: 3 questions (ii)

• Cranial trauma
• Severe psychiatric conditions
• Abuse of psychotropic drugs
• Alcohol abuse
• Sequelae from previous CNS-OIs or other neurological diseases

IADL questionnaire

Abnormal

NP Examination (iii)

Abnormal

NP examination will have to include tests exploring the following cognitive domains: fluency, executive functions, speed of information processing, attention/working memory, verbal and visual learning, verbal and visual memory, motor skills (ref. Antinori et al., Neurology 2007). Neurological examination

Brain MRI

CSF examination (iv)

Additional causes of NCI other than HIV excluded

HAND diagnosis (HAD, MND) (v)
International HIV Dementia Scale

Memory-Registration – Give four words to recall (dog, hat, bean, red) (in Luganda: kopo, engatto, doodo, myufo)—1 second to say each. Then ask the patient all four words after you have said them. Repeat words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later.

1. Motor Speed: Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.
   - 4 = ≥ 15 in 5 seconds
   - 3 = 11-14 in 5 seconds
   - 2 = 7-10 in 5 seconds
   - 1 = 3-6 in 5 seconds
   - 0 = 0-2 in 5 seconds

2. Psychomotor Speed: Have the patient perform the following movements with the non-dominant hand as quickly as possible:
   1) Clench hand in fist on flat surface. 2) Put hand flat on surface with palm down. 3) Put hand perpendicular to flat surface on the side of the 5th digit. Demonstrate and have patient perform twice for practice.
   - 4 = 4 sequences in 10 seconds
   - 3 = 3 sequences in 10 seconds
   - 2 = 2 sequences in 10 seconds
   - 1 = 1 sequence in 10 seconds
   - 0 = unable to perform

3. Memory-Recall: Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); color (red).
   Give 1 point for each word spontaneously recalled.
   Give 0.5 points for each correct answer after prompting
   Maximum – 4 points.

Total International HIV Dementia Scale Score
This is the sum of the scores on items 1-3. The maximum possible score is 12 points. A patient with a score of ≤10 should be evaluated further for possible dementia.

(Sacktor et al. AIDS 2005; 19:1367-1374)
HIV/AIDS EPIDEMIC - GALATI COUNTY

Yearly distribution of the new diagnosed cases: 01.12.2014

Peculiarity: 2 Epidemic patterns
- pediatric group: cohort (1988-1990)
- Adult group: cases infected in adult age

- No. cumulative cases (1990-2014) ......................... 737
  - Deaths.......................................................... 340
  - Alive............................................................ 397
  ➢ No. Patients with active ARVT............................. 258
Causes of Deaths in Galati County (2010-2015)

Opportunistic diseases

Neurologic diseases
- 4 LEMP
- 3 Neuro-Toxoplasmosis
- 3 TB-ME
- 2 cryptococcal ME
- 2 lymphoma
- 2 brain metastasis (lung cancer)
- 1 Primary brain tumor
- 1 bacterial ME

HAND
- 2 accidents
- 2 heart attacks
- 1 non-AIDS related cancer

16 Non-Adherent
14-Very Late presenters
3 Other

- Opportunistic infection of the central nervous system raised the risk of death more than 5 times.
- HAND tripled the death risk.
- Diagnosis of any neurologic disorder doubled the risk of death.

Variation of “Neuro-AIDS” group of patients

- Lost evidence: 9
- Deaths: 8
- Prison: 3
- Spain: 3
- Italy: 10
- UK: 9
- Germany: 2
- Austria: 1
- Greece: 1

77.3% Follow up the medical care in our clinic

2010: 203p

2014: 158p
### Demographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>Pediatric pattern (N=139)</th>
<th>Adult pattern (N=64)</th>
<th>X2-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of HIV dg.:&lt;5y/5-10y/&gt;10y</td>
<td>0 /22/129</td>
<td>14/36/14</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Median age:</td>
<td>26 [23; 82]</td>
<td>37 [23; 82]</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Sex: M/F:</td>
<td>69/70</td>
<td>30/34</td>
<td>OR=1.11; p=0.71</td>
</tr>
<tr>
<td>Living area U/R:</td>
<td>68/71</td>
<td>34/30</td>
<td>OR=1.22; p=0.577</td>
</tr>
<tr>
<td>Education level &lt; 4 years: 53/150</td>
<td>42/97</td>
<td>11/53</td>
<td>OR=2.04; p=0.050</td>
</tr>
<tr>
<td>Institutionalized</td>
<td>21/118</td>
<td>1/63</td>
<td>OR=11.21; p=0.003</td>
</tr>
<tr>
<td>Marital status: Single/ Couple</td>
<td>75/64</td>
<td>19/44</td>
<td>OR=2.69; p=0.001</td>
</tr>
<tr>
<td>Partner status: +/-</td>
<td>33/16</td>
<td>13/19</td>
<td>OR=3.014; p=0.017</td>
</tr>
<tr>
<td>Unknown status of partner</td>
<td>15/64</td>
<td>12/44</td>
<td>P=0.651</td>
</tr>
<tr>
<td>Children care 78/125</td>
<td>33/106</td>
<td>45/64</td>
<td>OR=7.6; p&lt;0.001;</td>
</tr>
<tr>
<td>Smoking 106/97</td>
<td>71/68</td>
<td>35/29</td>
<td>OR=1.15; p=0.632</td>
</tr>
<tr>
<td>Alcohol 37/166</td>
<td>26/113</td>
<td>11/53</td>
<td>OR=1.10; p=1.794</td>
</tr>
</tbody>
</table>
### Characteristics of HIV patients

<table>
<thead>
<tr>
<th></th>
<th>Pediatric pattern (N=139)</th>
<th>Adult pattern (N=64)</th>
<th>2T-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS 169/34</td>
<td>126/13</td>
<td>43/21</td>
<td>OR=4.73; p&lt;0.001</td>
</tr>
<tr>
<td>Undetectable ARN-HIV: 136/ 67</td>
<td>93/ 46</td>
<td>43/ 21</td>
<td>OR=0.98; p=0.096</td>
</tr>
<tr>
<td>HTA 20/183</td>
<td>9/130</td>
<td>11/53</td>
<td>OR=2.99; p=0.017</td>
</tr>
<tr>
<td>HCV 3/200</td>
<td>0/139</td>
<td>3/61</td>
<td>OR=0; p=0.010</td>
</tr>
<tr>
<td>HBV 56/147</td>
<td>51/88</td>
<td>5/59</td>
<td>OR=6.83; p&lt;0.001</td>
</tr>
<tr>
<td>2T-Test</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mann-Whitney Test</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadir CD4 Med=157/mm3</td>
<td>140/mm3</td>
<td>242/mm3</td>
<td>P=0.002</td>
</tr>
<tr>
<td>Current CD4 583 /mm3</td>
<td>583 /mm3</td>
<td>575 /mm3</td>
<td>P=0.541</td>
</tr>
<tr>
<td>Δ Current – Nadir CD4 : 338/mm3</td>
<td>372 /mm3</td>
<td>273 /mm3</td>
<td>P=0.197</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mann-Whitney Test</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tot. S-Ca Median =9.6mg/dl</td>
<td>9.69</td>
<td>9.45</td>
<td>p=0.027</td>
</tr>
<tr>
<td>S-Mg Median=1,98mg/dl</td>
<td>1.96</td>
<td>2.04</td>
<td>p=0.005</td>
</tr>
<tr>
<td>Vit D Median=22 mg/dl</td>
<td>21.3</td>
<td>17.9</td>
<td>p=0.028</td>
</tr>
<tr>
<td>Triglycerides Median=123 mg/dl</td>
<td>111.8</td>
<td>155.6</td>
<td>P=0.729</td>
</tr>
<tr>
<td>Glycemia Median=94.3 mg/dl</td>
<td>94.3</td>
<td>94.3</td>
<td>P=0.592</td>
</tr>
<tr>
<td>Hb Median=14.2g/dl</td>
<td>14.12</td>
<td>14.45</td>
<td>P=0.683</td>
</tr>
</tbody>
</table>
CNS Penetration Scores Of ART

Letendre  CNS score

<table>
<thead>
<tr>
<th></th>
<th>2010/11</th>
<th>2013/14</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1=</td>
<td>203</td>
<td>N2=158</td>
</tr>
<tr>
<td>Av=</td>
<td>7.86</td>
<td>Av=8.14</td>
</tr>
<tr>
<td>61% &gt;7</td>
<td></td>
<td>70.8% &gt;7</td>
</tr>
</tbody>
</table>

- 28% 5%
- 23%
- 35%
- 28%
- 5% 3%
Confounding factors/ exclusion criteria

<table>
<thead>
<tr>
<th></th>
<th>Low education</th>
<th>OI</th>
<th>Cranial Trauma</th>
<th>Alcohol</th>
<th>Severe psychiatric</th>
<th>Drugs</th>
<th>Hep-C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult</strong></td>
<td>11</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Pediatric</strong></td>
<td>42</td>
<td>16</td>
<td>7</td>
<td>14</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Exclusion criteria rate 30% (61/203)
The dynamic of NCD screening test (3Q)

<table>
<thead>
<tr>
<th></th>
<th>Pediatric-I</th>
<th>Pediatric -II</th>
<th>Adult -I</th>
<th>Adult -II</th>
</tr>
</thead>
<tbody>
<tr>
<td>3Q-0</td>
<td>66</td>
<td>49</td>
<td>34</td>
<td>26</td>
</tr>
<tr>
<td>3Q-1</td>
<td>23</td>
<td>40</td>
<td>15</td>
<td>23</td>
</tr>
</tbody>
</table>

P<0.001

+19%

+16.3%

44.6% NCI (2014);
16.8% progressive NCI in the last 2 y

**NCI screening: 3 questions**
1. Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)?
2. Do you feel that you are slower when reasoning, planning activities, or solving problems?
3. Do you have difficulties paying attention (e.g. to a conversation, book or movie)?

For each question, answers could be: a) never, b) hardly ever, or c) yes, definitely. HIV-positive persons are considered to have an “abnormal” result when answering “yes, definitely” on at least one question.
Depression in HIV patients from Galati

Challenges:

- Depressive mood is changing along the time
- Overlap in signs and symptoms of HIV disease and depression
- Symptoms such as anorexia, weight loss, fatigue, insomnia difficult to attribute to either depression or HIV/OI
Reasons for depression or transient depression

- Depression - Social reject: $p=0.005$
- Transient depression - Partner reject: $p=0.028$

Median IQ (pediatric)
No > Transient > Depression
90.5 > 81.5 > 71.5
The Dynamic of iHDS Screening Test

<table>
<thead>
<tr>
<th></th>
<th>Memory</th>
<th>Finger tapping</th>
<th>Coordinating task</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2010/11</strong></td>
<td>3.55</td>
<td>3.27</td>
<td>3.36</td>
</tr>
<tr>
<td><strong>2013/14</strong></td>
<td>3.43</td>
<td>2.82</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Av. Score

- **iHDS**
  - 2013/14
  - 2010/11
Comparative Median and Average Scores of HDS Items

- Memory
- Finger tapping
- Sequential motor task

Pediatric Adult

Comparative Median and Average Scores of HDS Items

<table>
<thead>
<tr>
<th>iHDS Score</th>
<th>9.6</th>
<th>9.8</th>
<th>10</th>
<th>10.2</th>
<th>10.4</th>
<th>10.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Comparative Dynamic of HDS In Pediatric and Adult HIV Groups

<table>
<thead>
<tr>
<th></th>
<th>Pediatric-I</th>
<th>Pediatric -II</th>
<th>Adult -I</th>
<th>Adult -II</th>
</tr>
</thead>
<tbody>
<tr>
<td>iHDS&lt;10</td>
<td>21</td>
<td>44</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>iHDS&gt;=10</td>
<td>71</td>
<td>48</td>
<td>30</td>
<td>25</td>
</tr>
</tbody>
</table>

- **Pediatric-I**: 21 iHDS<10, 71 iHDS>=10
- **Pediatric -II**: 44 iHDS<10, 48 iHDS>=10
- **Adult -I**: 19 iHDS<10, 30 iHDS>=10
- **Adult -II**: 24 iHDS<10, 25 iHDS>=10

- **P=0.020**
- **22.8%** 47.8% 38.7% 48.9%
Correlation of 3Q Test and iHDS Test

- iHDS-1: >10 (normal)
- iHDS-2: 8-10 (mild disfunction)
- iHDS3: <8 (severe disfunction)

### Correlation Results

- OR = 4.15, P < 0.001
- OR = 1.11, P = 0.920

### No. patients

<table>
<thead>
<tr>
<th>Group</th>
<th>3Q-0</th>
<th>3Q-1</th>
<th>3Q-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>iHDS&gt;=10</td>
<td>82</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>iHDS (10; 8]</td>
<td>20</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>iHDS&lt;8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Correlation of iHDS and depression

- No depression
- Transient depression
- Depression

Median HDS

<table>
<thead>
<tr>
<th>No depression</th>
<th>Transient depression</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>10.5</td>
<td>9</td>
</tr>
</tbody>
</table>

P values:
- P=0.902
- P<0.001
- P<0.001
Correlations of NCD Tests and HIV Markers

<table>
<thead>
<tr>
<th></th>
<th>ARN-HIV (det/undet)*</th>
<th>nadir CD4</th>
</tr>
</thead>
<tbody>
<tr>
<td>3Q-test</td>
<td>p=0.151</td>
<td>p=0.300</td>
</tr>
<tr>
<td>iHDS</td>
<td>p=0.677</td>
<td>p=0.020</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>p=0.627</td>
</tr>
<tr>
<td>➢ Transient: OR=3.13; p=0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ No: OR=2.08; p=0.143</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

➢ ARN-HIV – CNS penetration score: p<0.001

*baseline ARN-HIV was not systematically available

HAND in HAART Era
Occurs at higher CD4 counts
Course stable or oscillating
Occurs with undetectable plasma VL

Letendre et al, 16th CROI 2009, Abstract 484b
Does CNS penetration profile matter?

NO effect on 3Q, iHDS or depression

- **Sacktor N, 2001**: no effect on cognitive function
- **Cysique L, 2004**: effect only in cognitively impaired
- **Marra C., 2009**: CNS penetration associated with lower CSF HIV RNA but worse cognitive performance
- **Letendre S., 2007**: new index of penetration

Correlations of NCI variation by screening tests

- $\Delta 3Q \leftrightarrow \Delta iHDS$, $P<0.001$
- $\Delta 3Q \leftrightarrow \Delta$ Depression/Beck inventory, $P=0.019$
- $\Delta iHDS \leftrightarrow \Delta$ Depression/Beck inventory, $P=0.024$
- $\Delta$ Depression/Beck inventory \(\rightarrow\) HTA, $P=0.042$
- Age \(\rightarrow\) HTA, $P=0.011$
- HTA \(\rightarrow\) Adult group
- Adult group \(\rightarrow\) Pediatric group
- Pediatric group \(\rightarrow\) $\Delta$ Depression/Beck inventory
- $\Delta$ Depression/Beck inventory \(\rightarrow\) $\Delta 3Q$, $P<0.001$

Adult group

Pediatric group
Discussions

Limits:

• Shotcoming of more comprehensive reference NP tests
• Low performance of screening instrument as iHDS (Brunett J, 2013).
• Deepening investigations as HIV-VL in CSF, MRI or complex NC tests were achieved by few of our patients.
• The reasons for incomplete protocol:
  – High costs of MRI;
  – Difficulties to obtain the consent for lumbar puncture;
  – Refuse to go in other setting to be hospitalized.

Challenges for improving early detection of HAND:

– To use biomarkers for detection of predisposition, diagnostic and monitoring;
– To develop more accurate NP tests.
Conclusions

1. The frequency of NCD according to screening tests is 44% (3Q) and 48% (iHDS), consistent with other studies (Heaton, 2010).
2. Along the 4 years, screening tests mark the progression of NCD.
3. Most patients with NCD have mild dysfunctions.
4. The adult group is more severely affected due to the old age and more frequent hypertension, while the pediatric group seems to be faster impaired.
5. The results of NC screening tests are not influenced by HIV current markers or CNS penetration score.
6. IHDS score correlates with nadir CD4, as a hallmark of neurological damages established before initiation ARVT.
7. Mild cognitive impairment associated with HIV requires to improve screening tools and treatment interventions in order to improve the care and the quality of life for individuals living with HIV and AIDS.
References


Thank you!

Galati, Danube River