Classification of Pediatric HIV CNS Disease: Comparison of CNS and Systemic Disease Markers of Children Treated in the HAART Era

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Background

- HAART has altered the course of pediatric HIV disease

- Progressive encephalopathy, an early, common, and devastating manifestation of HIV infection has practically disappeared with the availability of HAART

- Questions remain about the prevalence and manifestations of HIV CNS disease in children, especially as they enter the 2nd and 3rd decades of life and are treated with HAART
Objective

• To characterize CNS disease in a cohort of HIV-infected children and adolescents, utilizing a classification scheme for pediatric HIV CNS disease
Methods

• Location: Pediatric HIV clinic at the NCI, NIH, Bethesda, MD

• Sample: All active pediatric HIV patients (N=77)

• Cross-sectional analysis of data (neurobehavioral, neuroimaging, psychiatric, educational, and medical) from their last clinic visit (2/02 – 1/05) in which an intelligence test was administered
CNS classification

- CNS status was classified according to specific criteria (Wolters & Brouwers, 1998) as either encephalopathic, CNS compromised, or not compromised
- Based on data from neuropsychological testing, neuroimaging, and neurologic exams
Encephalopathy - criteria

- Loss of previously-acquired skills and/or behaviors
- Significantly abnormal neurologic exam with functional deficits
- Cognitive test scores in the borderline/delayed range with functional deficits
- Significant drop in cognitive test scores, generally to the borderline/delayed range with functional deficits
- Significant improvement in cognitive test scores over approximately a six-month period associated with a new treatment when baseline scores are in the borderline to delayed range (retrospective classification)
CNS Compromised - criteria

- Abnormal neurologic findings but not significantly affecting function
- Cognitive test scores within normal limits (low average range or above) with no significant functional deficits and moderate to severe brain imaging abnormalities consistent with HIV-related changes
- Cognitive scores in the borderline range, with no significant functional deficits
- Significant drop in cognitive test scores, but generally still above the delayed range, with no loss of skills and no functional deficits
- Significant improvement in cognitive test scores over approximately a six month period associated with a new treatment when baseline scores are in the low average to average range and no brain imaging abnormalities (retrospective classification)
Not CNS Compromised - criteria

- Cognitive test scores within or above normal limits with no significant functional deficits or decline in cognitive test scores, a normal neurologic exam, and no significant brain imaging abnormalities
Cognitive Assessment

• Age appropriate test of general cognitive function:
  – Wechsler Intelligence Scale for Children-3rd edition
    • 6 - 16 years of age
    • Composite standard score: Full scale IQ (mean 100; SD = 15)
  – Wechsler Adult Intelligence Scale-3rd edition
    • 16 years and older
    • Composite standard score: Full scale IQ (mean 100; SD = 15)
QOL assessment

- Impact of Pediatric Illness (IPI) Scale: A comprehensive pilot QOL measure assessing four theoretical domains:
  - Adaptive behavior (school attendance, social activities, daily living skills)
  - Psychological/emotional functioning (anxiety, depression, self-esteem)
  - Physical/medical status (fatigue, pain, treatment side effects)
  - CNS symptoms (attention, memory, learning problems)
- Administered to the parent of children 6 to 18 years of age at the time of the cognitive assessment
- Yields mean domain and total scores
Neurologic Exam

• Standard pediatric neurologic exam assessing function in 7 domains:
  – Cranial nerves, cerebellar, motor, extrapyramidal, deep tendon reflexes/plantar responses, gait, and head size

• Neurologic abnormalities coded as a 1 if present and 0 if absent

• Summary score indicates number of abnormalities present (0 - 31)
CT Brain Scans

- Pediatric neurologist, blinded to the name and status of the patient, rated the CT brain scans:
  - For presence and severity of brain abnormalities
    - Ventricular enlargement, subarachnoid dilatation, white matter hypodensity, calcifications, other, and overall severity
  - Using a 100 mm visual analog scale (DeCarli et al, 1993)
  - High interrater reliability ($r = .86; p < .0001$)
Results

- Total Sample \( N = 77 \)
- Mean age (range) = 15.2 years (7.2 – 25.3 years)
- 95% (73/77) were on HAART regimens, containing either a PI or NNRTI
- 42% classified as either encephalopathic (\( N = 18 \)) or CNS compromised (\( N = 14 \))
- 39% with psychiatric diagnosis
Results by CNS Classification

Mean age

- Encephalopathic
- CNS compromised
- Not compromised
Results by CNS Classification

Full Scale IQ

- Encephalopathic
- CNS compromised
- Not compromised
Results by CNS Classification

Brain CT Rating

- Encephalopathic
- CNS compromised
- Not compromised
Results by CNS Classification

Neurologic exam

[Bar chart with categories Encephalopathic, CNS compromised, Not compromised]
## Psychiatric Results

<table>
<thead>
<tr>
<th>Psychiatric dx (%)</th>
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<tbody>
<tr>
<td>Enceph (N=18)</td>
<td>9 (50)</td>
</tr>
<tr>
<td>CNS Comp (N=14)</td>
<td>5 (36)</td>
</tr>
<tr>
<td>Not Comp (N=45)</td>
<td>16 (36)</td>
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<tr>
<td>TOTAL (N=77)</td>
<td>30 (39)</td>
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<table>
<thead>
<tr>
<th>ADHD</th>
<th>Depression</th>
<th>Anxiety</th>
<th>Bipolar</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>TOTAL</td>
<td>18</td>
<td>7</td>
<td>4</td>
<td>1</td>
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Special Education

![Bar chart showing the distribution of encephalopathic, CNS compromised, and not compromised cases.]

Legend:
- Red: Encephalopathic
- Green: CNS compromised
- Blue: Not compromised
Conclusions

- CNS disease is still prevalent in pediatric patients in the HAART era, even in school-age children and adolescents.
- They exhibit cognitive deficits that may require special education and impact QOL.
- High rates of psychiatric disorders are present but the relation to HIV CNS disease is unclear.
- Neurocognitive outcomes should be measured in all pediatric studies of antiretroviral therapy.
- Strategies for targeting HIV CNS disease in children need to be developed.
Acknowledgements

• Pim Brouwers
• Robert Yarchoan
• Pediatric HIV Working group of the HIV & AIDS Malignancy Branch, NCI