HIV/AIDS and Neurodevelopment in sub-Saharan Africa.

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BRAIN DISORDERS IN THE DEVELOPING WORLD: RESEARCH ACROSS THE LIFESPAN
Introduction:
review of experiences in US, Europe and Africa
HIV infection and CNS in children

- HIV infection impairs the development and growth of an immature CNS

- CNS involvement presents as HIV encephalopathy with developmental delay or loss of developmental milestones (motor, mental and expressive language), microcephaly, and pyramidal tract symptoms (Belman, Diamond et al. 1988)

- HIV CNS involvement can occur before significant immunosuppression and is the first AIDS defining illness in as many as 18% of pediatric patients (Gabuzda and Hirsch 1987; Vincent 1989)
HIV infection and CNS in children

• Broad **variability** in severity and timing (Wachtel 1993, Epstein 1986, Lobato 1995)

• **Highest incidence** rate of HIV-related CNS manifestations in first two years of life:
  – 10% incidence rate in the first year of life,
  – 4% incidence rate in the second year of life
  – <1% incidence rate the in the third year of life and thereafter.
  – Cumulative 7y incidence post-infection: 16% in children vs. 5% in adults

(Epstein, Sharer et al. 1986; Lobato, Caldwell et al. 1995; Tardieu, Le Chenadec et al. 2000)
Risk factors for pediatric neuroAIDS

- **Timing of infection**: children with intra-uterine infection are more likely to develop severe cognitive and motor delay, show earlier onset of neurobehavioral delay, and have more rapid progression of HIV-related encephalopathy (Pollack, Kuchuk et al. 1996; Smith, Malee et al. 2000)

- **Advanced maternal disease at delivery** - as measured by CD4+ cell count and viral load (Blanche, Mayaux et al. 1994)


- **High plasma viral load in infancy** – not predictive of the age at onset of CNS manifestations (Pollack, Kuchuk et al. 1996; Cooper, Hanson et al. 1998; Lindsey, Hughes et al. 2000)

- **Environmental factors** such as quality of the home environment and socio-economic status (Coscia, Christensen et al. 2001; Kullgren, Morris et al. 2004)
HIV infection and CNS in children and HAART

• Prevalence of PHE in pre-HAART era in the USA:
  – 13-35% of children with HIV infection and
  – 35-50% of children diagnosed with AIDS
    (Gabuzda and Hirsch 1987; Lobato, Caldwell et al. 1995; Blanche, Newell et al. 1997; Cooper, Hanson et al. 1998; Tardieu, Le Chenadec et al. 2000)


• Access to HAART has led to a dramatical decrease in the incidence of active PHE to 1.6% (Chiriboga, Fleishman et al. 2005)
HIV and Neurodevelopment: experience from Africa

• Msellati et al, 1993, Rwanda (n=20-43, age 0-24 m)
  – Deliberately very simple screening tool
  – HIV infected children perform poor compared to HIV exposed infants

• Boivin et al. 1995, Zaire (n=11/15/15, age 3-18 m)
  – Portions of the Early Childhood Screening Profiles (cognitive, language, motor) and Kaufman Assessment Battery (cognitive)
  – HIV infected children demonstrate global cognitive impairment beyond the indirect effects of maternal illness
  – Spatial memory and motor functions were the most affected
HIV and Neurodevelopment: experience from Africa

- Drotar et al. 1997 and 1999, Uganda (61 HIV infected; 234 HIV exposed; 115 control, age 6-24m)
  - Bayley scales (1st edition), and Fagan test of intelligence
  - More frequent and earlier onset of motor deficits compared to delay in mental development, deceleration in their rate of motor development
  - No delay in development among HIV exposed uninfected infants when compared to control children

- Bagenda, Nassali et al. 2006, Uganda (follow up of the Drotar cohort (n=28, age 6-12 years)
  - no delay in neurologic, motor and psychometric development compared to age- and gender-matched sero-reverters and controls.
  - subgroup of HIV-infected children for whom progression of HIV disease is less aggressive? (no HAART available)
HIV and Neurodevelopment: experience from Africa

- McGrath et al. 2006, Tanzania, breast fed children born to HIV-infected mothers (n=327, birth-18 months)
  - Bayley Scales (2nd edition) at 6, 12 and 18 months
  - Infected and exposed, uninfected children had slower mental and motor development than expected for their age
  - Children infected early (first 21 days of life) were most affected
  - Standardized scores for all children decreased with increasing age, suggesting a cumulative risk of poor neurodevelopment caused by poverty the burden on a family of caring for HIV infected individuals and HIV infection
Conclusion
HIV and Neurodevelopment: experience from Africa

- Children **age 0 – 24 months** (4 studies)
  - HIV infected children perform poorly, motor > mental
  - Conflicting results for HIV exposed uninfected children
  - Impact of socio-economic factors
  - Infection in first 21 days of life = risk factor

- Children **age > 24 months** (1 study)
  - No neurodevelopmental delay ??
Assessing neurodevelopmental outcome in African children: a challenge

- Few neurodevelopmental assessment tools have been evaluated and validated outside of the US and Europe.
- Capacity in neurodevelopmental assessment is limited
- How can one disentangle the direct effect of HIV on the CNS from environmental and social impact of HIV on the neurodevelopment of HIV infected children in the sub-Saharan African context?
Pilot study in Kinshasa, DRC
### HIV/AIDS estimates for DRC 2005

<table>
<thead>
<tr>
<th></th>
<th>Adults and children living with HIV</th>
<th>Children (0-14) living with HIV</th>
<th>Adults (15-49) rate (%)</th>
<th>AIDS deaths in Adults and Children</th>
<th>Orphans (0-17) due to AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Democratic Republic of Congo</td>
<td>1,000,000 (560,000-1,500,000)</td>
<td>120,000 (40,000-270,000)</td>
<td>3.2 (1.8-4.9)</td>
<td>90,000 (47,000-150,000)</td>
<td>680,000 (380,000-1 million)</td>
</tr>
</tbody>
</table>

Pilot Study Design

• Three groups of children age 18 – 71 months
  – 35 HIV infected children initiating HAART
  – 35 HIV affected children (AIDS orphans and children of parents with symptomatic AIDS)
  – 90 control (HIV unexposed healthy) children living with healthy parents (5 boys and 5 girls for every 6 month age class between 18 and 71 m) - Kinshasa and Cape Town

• Data collection at baseline, 6 and 12 m follow-up
  – Neurodevelopmental assessment
  – Maternal quality of life
  – Demographic parameters and family structure
  – Clinical and immunological parameters
Selection of neurodevelopmental tools

• Criteria for selection
  • Age specific tools
  • Valid and reliable
  • Cross-cultural utility

• 18 months – 30 months:
  • Bayley 2\textsuperscript{nd} edition (mental, motor and behavior)
  • Rossetti (Interaction-Attachment, Pragmatics, Gesture, Play, Language Comprehension, and Language Expression)

• 30 months – 72 months:
  • SON-R 2.5-7 (mental)
  • Peabody (motor)
  • Rossetti (language)
Strength and weaknesses of tools

- **Bayley and Peabody**: valid and standardized, but not in DRC.
- **Rossetti**: Less dependant on the language itself as direct observation, elicited behavior, and caregiver’s report equally credit the child’s performance. Not validated, no standardized score. Gesture and play are influenced by the general status (weakness).
- **Snijders-Oomen Nonverbal Intelligence Test (SON-R 2½-7)**: A nonverbal, language independent tool comprised of six subtests. Two subtests (puzzles and analogies) were eliminated for the “Africa version”. The 4 remaining tests are situations, mozaics, categories and patterns. Validated and standardized, but not in DRC.
Nonverbal Intelligence Test (SON-R) 2½-7: Challenges

- **Mosaic**: poor knowledge of colors
- **Categories and situations**: certain items are not recognized by the child and need modification for the African context

<table>
<thead>
<tr>
<th>cake</th>
<th>bread</th>
</tr>
</thead>
<tbody>
<tr>
<td>pear</td>
<td>mango</td>
</tr>
<tr>
<td>strawberry</td>
<td>pineapple</td>
</tr>
<tr>
<td>dromedary</td>
<td>antelope</td>
</tr>
<tr>
<td>sheep</td>
<td>goat</td>
</tr>
<tr>
<td>rabbit</td>
<td>chicken</td>
</tr>
<tr>
<td>Dalmatian dog</td>
<td>Street dog</td>
</tr>
<tr>
<td>Black &amp; white cow</td>
<td>Brown cow</td>
</tr>
<tr>
<td>gymnastics</td>
<td>soccer</td>
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</tbody>
</table>
Results Part 1: Validity of assessment tools in the African context

- 90 control children in Kinshasa, DRC
  - Bayley motor scale
  - Bayley mental scale
  - Peabody motor scale
  - SON 2½-7

- 90 control children in Cape Town, SA
  - SON 2½-7
Bayley Scales of Infant Development, Psychomotor Development Index (PDI)

- Control Group, mean score 94.1
- Standard Scores, mean score 100
Bayley Scales of Infant Development

Mental Development Index (MDI)

Control Group, mean score 85.3

Standard Scores, mean score 100
Peabody Developmental Motor Scales,
Total Motor Quotient (TMQ)

- Control Group, mean score 99.2
- Standard Scores, mean score 100
SON-R 2.5-7, SON-IQ mental

Control Group, mean score 84.6
Cape Town Validation Group, mean score 82.6
Standard Scores, mean score 100
Conclusions: validity of tools

• Normal distribution

• Mean and SD of the scales for motor development for the control group was not significantly different from the mean and SD of the normative populations.

• There is a shift to the left for the mental development assessment tools. This may be improved by adapting some of the pictures to the sub-Saharan African context.
Results part 2: Developmental Assessment of HIV infected & affected children

- 35 HIV infected children prior to start ART
- 35 HIV affected children (AIDS orphans and children of parents with symptomatic AIDS)
- 90 control (HIV unexposed healthy) children with healthy parents
Baseline data: motor development

Age 18-29 months (Bayley)

Age 30-71 months (Peabody)
Baseline data: mental development

Age 18-29 months (Bayley)

Age 30-71 months (SON)
Baseline: behavioral development

Children age 18-29 months (Bayley) no data on older children
Baseline: language development

Language comprehension

Language expression

Rossetti (age 18 - 71 months)
Baseline: comparison of motor and mental development in children aged 18-29 months

<table>
<thead>
<tr>
<th></th>
<th>HIV infected n=11</th>
<th>HIV affected n=13</th>
<th>Control n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Mental Development</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayley MDI</td>
<td>46.5 (23.4)</td>
<td>74.5 (12.5)</td>
<td>85.3 (18.0)</td>
</tr>
<tr>
<td>Motor Development</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayley PDI</td>
<td>33.5 (36.1)</td>
<td>75.9 (18.9)</td>
<td>94.1 (13.1)</td>
</tr>
</tbody>
</table>

HIV infected vs. HIV affected

<table>
<thead>
<tr>
<th></th>
<th>HIV infected vs. HIV affected</th>
<th>HIV infected vs. Control group</th>
<th>HIV affected vs. Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI (mental)</td>
<td>0.001</td>
<td>0.0001</td>
<td>0.07</td>
</tr>
<tr>
<td>PDI (motor)</td>
<td>0.005</td>
<td>&lt;0.0001</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Baseline: motor and mental development in children aged 30-71 months

<table>
<thead>
<tr>
<th>Mental Development</th>
<th>HIV infected n=24 Mean (SD)</th>
<th>HIV affected n=22 Mean (SD)</th>
<th>Control n=70 Mean (SD)</th>
<th>Cape Town n=70 Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SON</td>
<td>71.2 (18.2)</td>
<td>75.2 (23.4)</td>
<td>84.6 (22.4)</td>
<td>82.6 (12.9)</td>
</tr>
<tr>
<td>Motor Development</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMQ</td>
<td>83.6 (10.8)</td>
<td>93.6 (9.3)</td>
<td>99.2 (7.9)</td>
<td></td>
</tr>
</tbody>
</table>

HIV infected vs. HIV affected
HIV infected vs. Control group
HIV affected vs. Control Group
DRC Control group vs. Cape Town group

<table>
<thead>
<tr>
<th></th>
<th>HIV infected vs. HIV affected</th>
<th>HIV infected vs. Control group</th>
<th>HIV affected vs. Control Group</th>
<th>DRC Control group vs. Cape Town group</th>
</tr>
</thead>
<tbody>
<tr>
<td>SON (mental)</td>
<td>0.6</td>
<td>0.01</td>
<td>0.07</td>
<td>0.5</td>
</tr>
<tr>
<td>TMQ (motor)</td>
<td>0.002</td>
<td>&lt;0.0001</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>
Correlation between mental and motor development scores – 18-29 m

Overall: $r = 0.84$
HIV infected: $r = 0.78$
HIV affected: $r = 0.70$
Control: $r = 0.68$
Correlation between mental and motor development scores – 30-70 m

overall: $r = 0.35$  
HIV affected: $r = 0.63$  
HIV infected: $r = 0.07$  
control: $r = 0.21$
Potential confounders & effect modifiers

Malnutrition (WAZ)

Socio-economic status
Motor and mental development – evaluation at 6 months follow up

Mental development

Motor development
Evaluation of mental and motor development over time in HIV infected children

Mental development

Motor development
Motor and mental development – evaluation at 12 months follow up

Mental development

Motor development
Conclusions:
Impact of HIV on neurodevelopment

- Motor, mental and language development is delayed in an overwhelming majority of HIV infected children.
- HIV exposed, affected children had significant delays in their motor development. The mental development tended to be slower but the difference was not statistically significant.
- The motor development of HIV infected children was significantly more delayed than that of HIV affected children, possibly indicating both a direct biological (HIV) and environmental component.
- Behavioral problems were identified in both HIV infected and affected children.
- Language expression was more delayed compared to comprehension.
Conclusions:
The role of age

- Impact was larger in the younger age group
  - Due to use of different tools in different age groups?
  - Younger children with neurodevelopmental problems are those infected in utero and/or those with rapid progression?
  - Effect of “survival cohort”?
Conclusions:
The role of ART

• Both mental development and motor development improved in a greater proportion of HIV infected children compared to control children = effect of ART

• Greater improvement of mental development scores compared to motor development scores in the control group = learning effect
Next steps

• Conduct a longitudinal community-based study of the epidemiology of PHE, and the effect of antiretroviral therapy on HIV-related CNS disease in young children.

• To characterization of HIV compartmentalization in the CNS in HIV infected infants at the time of ART initiation and a over time following ART initiation, using HTA (heteroduplex-tracking assay)

• Develop culturally relevant and sustainable early intervention strategies
Acknowledgements

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