Chapter 12
Cognitive Outcome of Malaria and HIV Infection in Children in Sub-Saharan Africa

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Abstract Infections of the Central Nervous System (CNS) are a public health burden for children in sub-Saharan Africa. In addition to their high mortality, they are a major cause of both major and subtle cognitive deficits in children. With the advent of more effective treatments, there is increased survival of these children meaning that more children who have suffered CNS infections are surviving into adulthood with consequent short or long term cognitive deficits. This chapter reviews the current literature on the cognitive deficits resulting from CNS malaria and HIV infection, the main causes of cognitive deficits in African children among the infectious diseases. It also looks at the factors associated with these cognitive deficits and reviews different interventions to prevent or improve outcome.

Keywords Central nervous system • Malaria • HIV/AIDS • Infection • Cognitive deficits • Rehabilitation

Introduction

Infections of the central nervous system are a public health burden for children in sub-Saharan Africa. In addition to their high mortality, they are a major cause of both major and subtle cognitive deficits in children. With the advent of more effective treatments, there is increased survival of these children meaning that more children are surviving into adulthood with short or long term cognitive deficits. This chapter reviews the current literature on the cognitive deficits resulting from malaria and HIV infection, the main causes of cognitive deficits in African children among the infectious diseases. It also looks at the factors associated with these cognitive deficits and reviews different interventions to prevent or improve outcome.

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S. Musisi, S. Jacobson (eds.), *Brain Degeneration and Dementia in Sub-Saharan Africa*, DOI 10.1007/978-1-4939-2456-1_12

Cognitive Outcomes of Malaria Infection in Children

During malaria infection, there is obstruction of blood through the capillaries due to sequestration of parasitized red blood cells, release of pro-inflammatory cytokines that affect the blood brain barrier integrity leading to metabolic derangement, seizures and coma [34]. Other less severe forms of malaria present with repeated seizures and impaired consciousness which can adversely affect the brain [16, 31]. In uncomplicated malaria and asymptomatic malaria, parasitemia present in the body may up-regulate hepcidin which in turn down-regulates iron absorption [19]. The resulting reduced iron intake and or unavailability is associated with a number of cognitive and behavioural problems [46]. The full spectrum of malaria illness from asymptomatic through symptomatic but non-severe malaria, to severe malaria (malaria with seizures and/or impaired consciousness, cerebral malaria) poses a potential risk to brain function leading to cognitive deficits. This review of the literature details the cognitive outcomes of the different forms of malaria and the risk factors.

Cognitive Outcome After Asymptomatic Malaria

Much emphasis has been placed on the severe forms of malaria due to their high mortality and resulting sequelae. Due to its role in malaria transmission, asymptomatic malaria, until recently has not been considered of much clinical concern, but it is now gaining important consideration [27]. High rates of asymptomatic malaria have been observed in African children with rates as high as 80 % in the wet seasons [27, 43]. Two studies have so far evaluated the effects of asymptomatic malaria on cognition in children.

In a study to assess the effect of asymptomatic malaria on cognition, Al Serouri et al. [1] compared 445 Yemeni children with asymptomatic malaria to 142 children matched for grade and school on tests of verbal fluency, working memory, sustained attention, psychomotor speed, fine motor coordination and visual recognition [1]. Two weeks later, 150 children still asymptomatic were compared to 150 children whose parasitemia cleared on the above tests. Regression analysis controlling for age, socioeconomic status and nutrition found fine motor coordination to be the only cognitive ability affected by asymptomatic malaria. Parasite density predicted fine motor coordination scores at baseline and improvement in visual recall after parasite clearance. No significant change in cognitive scores was noticed 2 weeks later between those who were still asymptomatic and those whose parasites cleared. Other factors associated with cognitive test performance were anemia, wealth factor and age. The authors concluded that parasitemia may affect fine motor skills and visual recall.

In a Ugandan study, Nankabirwa et al. [50] carried out a study to assess the association between anemia, asymptomatic malaria and cognition in Ugandan

school children aged 6–14 years [50]. They assessed sustained attention and abstract reasoning in 740 children as well as, sociodemographic variables, helminth infection and haemoglobin. About 30 % of the children had asymptomatic malaria. Multiple regression analyses controlling for sex, age, weight for age Z score, helminth infection, anemia, socioeconomic status and maternal education showed an association between asymptomatic malaria and sustained attention (adjusted mean difference: −1.6, 95 % CI: −2.49 to −0.81) and abstract reasoning (−0.6, 95 % CI: −1.01 to −0.21). Higher parasitemia was associated with lower attention scores. Unlike the study by Al Serouri et al. [1], anemia was not associated with any cognitive outcome in this study. They concluded that effect of asymptomatic malaria on cognition could be a result of repeated infections or an immunological pathway.

These studies suggest that asymptomatic malaria affects cognition in children though it is not clear how this occurs since both studies reported slightly differing results. In the Yemeni study, being anemic (haemoglobin ≤90 g/l) was associated with lower cognitive scores which was not the case in the Ugandan study. Nankabirwa et al. [50] showed that higher parasitemia affected sustained attention scores while Al Serouri et al. [1] reported that asymptomatic children who became parasite free 2 weeks later did not show an improvement in cognitive scores, implying that parasite presence is mostly likely not the main cause for low cognitive scores.

Cognitive Outcome After Non-severe Malaria

Fernando and colleagues have carried out a series of studies looking at the effect of uncomplicated malaria on cognitive outcome and school performance in children. They followed up 571 children aged 1–8 years for 6 years from 1992 and recorded the number of malaria episodes [26]. Children's scores in mathematics and language in 1997 were associated with the number of malaria episodes. Those who experienced three or less episodes scored 15 % higher than those with more episodes. These findings were replicated in a cross sectional study where they assessed the effect of repeated malaria attacks on measures of writing, reading skills, letter reading, sentence structure and mathematics in 325 children aged 4–6 years [25]. Children were tested at one time point and number of malaria episodes suffered in their life time recorded. Total number of malaria attacks was associated with letter reading and languages scores, where those not experiencing any malaria episode had scores 19 % higher than those who had five or more episodes for letter reading and 4.3 % for language. They later investigated the short term impact of an acute malaria episode on tests of mathematics and language where 199 children with malaria and 144 children with non malaria fever were tested at presentation to a health facility and 2 weeks later after treatment of the malaria bout [24]. A control group of 305 healthy children were also given the same tests. Children with malaria performed significantly poorer in mathematics and language at both time points compared to the controls. Those with non malaria fever also had poorer scores at

baseline but not at follow-up. Contrary to expected results, higher haemoglobin was associated with poorer scores in mathematics and language.

Recently Thuilliez and colleagues followed up 227 Malian children for 8 months recording malaria episodes, socioeconomic variables and cognition [55]. Children who had not experienced any malaria episode had better scores than those who had malaria in the follow-up period. In addition, higher parasitemia was associated with lower cognitive scores. The effect of anemia on cognition was however not conclusive. Malaria was also the most common cause of absenteeism from school.

Contrary to all the above findings, Halliday and colleagues did not observe any effect by either malaria infection or anemia during malarial illness on sustained attention, literacy, cognition or numeracy in 2,400 Kenyan children [29]. Other non-health related variables like age, gender, socioeconomic status, parental education and school environment were associated with cognitive outcomes suggesting health status (single malaria episode or anemia) may not be predictive of cognition in children in moderate malaria transmission areas after non-severe malaria.

Despite these findings from Halliday et al. [29], the preceding studies provide strong evidence that uncomplicated malaria affects cognition and academic performance in children with number of malaria episodes being the best predictor of outcome. The mechanisms for the effect on cognition are not clearly understood.

Cognitive Outcome After Complicated Malaria

Effect of Malaria with Impaired Consciousness on Cognition

Holding et al. assessed cognitive outcomes in 87 children who had malaria with impaired consciousness 42–70 months after the illness [31]. An equal number of age matched controls also completed the same battery of tests. More children in the malaria group were cognitively impaired (14 %) compared to 4 % in the control group with hypoglycaemia and coma score less than 2 independently associated with cognitive impairment. All children who had a coma score less than 2 were cognitively impaired. This group with a coma score less than 2 meets the criteria for cerebral malaria (CM) which makes it difficult to make conclusions about the effect of malaria with impaired consciousness on cognition. This is because some of those found to be impaired may have had a clear diagnosis of CM.

Effect of Malaria with Repeated Seizures on Cognition

Convulsions are a common feature in childhood malaria in African children and are predictive of neurological outcome and mortality [33, 32]. Carter et al. studied cognitive outcomes in 156 Kenyan children aged 6–9 years with a history of malaria with multiple seizures (MS) [16]. The median time from admission to

assessment was 71 months (IQR 55–85 months). An age matched group of 179 children without a history of MS were also enrolled as a control group. Children were given tests for speech and language, attention, motor skills, non-verbal skills, memory, hearing and vision and behaviour. Although the two groups did not differ much on most tests, 23.7 % of those with malaria had impairment in at least one of the above areas compared to 10.1 % in the controls. No effect was observed on memory in this study and in a later analysis of everyday memory in this same group [41].

In a subsequent study to assess speech and language functions after malaria with multiple seizures, Carter and colleagues administered tests for receptive grammar, receptive vocabulary, syntax, lexical semantics, higher level language, pragmatics and phonology and word finding [17]. The MS group had 9 % impaired in at least one of the areas tested compared to 2 % of the controls. The malaria group were three times more likely to develop speech and language impairment than the controls (OR = 3.12, 95 % CI = 0.9–10.8, p = 0.07).

These studies are evidence that MS is associated with cognitive, motor, behavioural and speech and language deficits in children. The above studies were carried out over 7 years after the illness in some of the children indicating the longterm effects of malaria with multiple seizures. The risk factors for these deficits were not identified although children with active epilepsy performed worse than those without epilepsy [16]. Active epilepsy is a likely consequence of severe malaria as surviving children tend to progressively have more seizures at 24 months [53].

Effect of Severe Malarial Anemia on Cognition in Children

Severe malarial anemia (SMA) is the commonest form of severe malaria affecting up to five million children annually [49]. Asymptomatic and uncomplicated malaria are associated with poor cognitive outcome in children as noted above. In addition, anemia is also associated with poor cognitive outcome [52]. This implies that SMA affecting several children in Africa could also be a major cause of cognitive deficits in children. In a recent study among Ugandan children aged 18 months to 4.9 years, neurocognitive test scores of a group that survived SMA was compared to community controls [6]. Attention, memory and overall cognition were assessed a week after discharge, and at 6 and 12 months. The SMA group had poorer scores in cognitive ability than the community controls. Attention scores were also lower but not significantly. The difference in age adjusted Z scores for overall cognition between the SMA group and community controls was half a standard deviation (−0.52) analogous to 8 IQ points. To our knowledge, this is the first study demonstrating the effects of SMA on cognition. It provides further evidence of malaria's effect on children's cognition as shown by the difference of about 8 IQ points 12 months after the illness.

Effect of Cerebral Malaria on Cognition in Children

The effects of CM on cognition have been studied more than any other malaria form. Cerebral Malaria (CM) is caused by P. Falciparum and is associated with alterations in consciousness, coma, convulsions and high fever. Retrospective studies show that neurocognitive deficits are common in children with a history of CM with coma duration, deep coma, multiple seizures on admission, duration of seizures, malnutrition and hypoglycaemia associated with these deficits [9, 22, 33, 40, 42]. Prospective studies have gone further to describe the progression of these sequelae in children. John and colleagues assessed memory, learning and attention at baseline, 3, 6 and 24 months in 44 children with CM compared to 54 with uncomplicated malaria [11, 36]. Scores were compared to 89 community controls. At 3 months, 19 % of the CM group were impaired in at least one of the three areas tested compared to 7 % of the controls ($p=0.07$). The impairment rate in the CM group increased at 6 months (21.5 % vs. 5.7 %, $p=0.01$) and at 24 months (26.3 % vs. 7.6 %, $p=0.006$) with attention being the most affected. Children with CM had a 3.67 fold increased risk of developing cognitive impairment compared to the controls [36].

This first prospective study of the cognitive sequelae of CM demonstrated that children with a history of CM have a slower developmental trajectory than their peers who had no CM. It also collaborates with earlier retrospective studies which showed long-term deficits after CM [16]. Factors associated with cognitive deficits at 6 months were coma duration and number of seizures while diminished tendon reflexes and neurological deficits at 3 months were associated with cognitive impairment at 24 months. Elevated CSF tumour necrosis factor alpha was correlated with attention and memory scores at 6 months [37].

Malaria retinopathy is now as a distinctive feature of CM that helps improve the diagnosis of the disease [7]. This is because children diagnosed with CM without malaria retinopathy have other pre-existing developmental delays and a family history of epilepsy [7] which may contribute to the cognitive deficits thus over estimating the cognitive burden of CM. Birbeck and colleagues carried out a prospective study to determine whether retinopathy confirmed CM is a risk factor for epilepsy and new neuro-disabilities [8]. They recruited 132 children with retinopathy confirmed CM and 264 controls (non comatose sick children) and followed them up for 544 days. The CM group were at increased risk for epilepsy (OR undefined, $p<0.00001$) and new neurodisabilities (OR 37.8, 95 % CI 8.8–161.8; $p<0.0001$). Further study of a sample of these children showed the CM group to have neurodevelopmental delay (OR 2.13, 95 % CI 1.09–4.19; $p<0.028$) especially in language [14]. Seizures during admission and high temperature were associated with epilepsy while platelet count, lactate and coma duration were associated with neurodevelopmental delay [8, 14].

A recent prospective study in Ugandan children below 5 years old assessed general cognition, memory and attention in children with CM a week after discharge and at 6 and 12 months later [6]. Test scores were compared to a group with SMA and a community control group. Children with CM had poorer scores in all domains

than the community control group at 12 months. The difference in age adjusted Z scores at 12 months between the CM group and the community controls was almost a full standard deviation (−0.85) analogous to 13 IQ points. Longer coma duration, deeper coma, number of seizures and neurologic deficits at 6 and 12 months were associated with lower cognitive outcomes. Presence of retinopathy did not affect the outcome as CM survivors with and without retinopathy did not differ in test performance and retinopathy did not modify the effect of CM on cognition.

These studies provide strong evidence that CM is associated with cognitive deficits in children which persist for some years after the illness. These deficits are also associated with clinical and laboratory factors involved in the disease pathogenesis implying adjuvant treatments targeting these factors may improve cognitive outcome.

Interventions to Prevent Cognitive Deficits or Improve Outcome After Malaria Infection

Primary Prevention

Primary prevention interventions will target prevention of malaria infection in order to remove the risk of these cognitive deficits. Malaria prevention approaches include; vaccination, vector control (insecticide-treated bed net use, indoor residual spraying), chemoprevention and chemoprophylaxis [58]. Chemoprevention reduces the incidence of malaria, parasitemia and anemia both of which are independently associated with poor cognitive outcome [51]. In Gambia, Jukes et al. assigned 1,190 children under 5 years of age to either chemoprophylaxis or placebo for 4 years during the malaria transmission season and followed up 14 years later [39]. No significant differences were seen in mental development scores between the treatment groups. Children who received chemoprevention achieved just over half a grade higher in school, a significant difference compared to controls. Clarke et al. assigned 6,758 children aged 5–18 years to intermittent preventive treatment (IPT) or a placebo [18]. At 12 months post intervention, the IPT group had a lower prevalence of anaemia and had higher attention scores than the placebo group. No trials have evaluated the effect of the other malaria prevention interventions on cognition.

Secondary Prevention

Secondary prevention of cognitive outcomes in children infected with malaria involves administration of effective treatments and or using adjunct therapies to combat disease processes associated with cognitive impairment. In severe malaria, artesunate is more effective than quinine in reducing mortality and also reducing

seizures and coma depth, two clinical features associated with poor cognitive outcome [20]. There was no significant difference in neurological outcome at 28 days between the groups. However trials for adjunct therapies for severe malaria have not been successful in reducing mortality, coma or seizures [38].

Tertiary Prevention

Children surviving severe malaria are at risk for cognitive impairment with 1 in 4 going on to have long term cognitive impairment [36]. Trials using computerised cognitive rehabilitation training in African children surviving CM have shown benefits in cognition and behaviour suggesting that interventions carried out after the disease may be beneficial [3, 5]. In these trials, children were assigned to 16 sessions, each last 45 min delivered over 8 weeks (two sessions per week). Children completed cognitive exercises training memory, attention, visuomotor and reasoning. These studies however did not have an active control group that was also exposed to computers, had no long term follow-up and it is not known which of the four categories of cognitive exercises are more effective or whether benefit can be obtained by training one skill as has been done successfully for ADHD [44]. Despite these limitations, they do improve cognition in children surviving severe malaria.

Effect of HIV on Cognition in Children

The HIV virus is transported into the brain through the blood brain barrier by infected monocytes which in turn differentiate into macrophages that reproduce the virus in the brain. Infected CD4 T lymphocytes may also transport the virus into the brain [28]. As a result of HIV entry in the brain, activated microglia and macrophage release quinolinic acid, tumor necrosis factor, platelet activating factor, and arachidonic acid metabolites which impair blood brain barrier function resulting in widespread inflammation in the brain [28, 23].

Cognitive Outcomes of HIV Infection in Antiretroviral Therapy (ART) Naive Children

The earliest studies on the effect of HIV on African children's cognition were carried out in the pre-ART era. Msellati and colleagues in Rwanda compared neurodevelopmental outcome (gross motor, fine motor, social contact and language) of perinatally HIV infected children to two control groups; HIV negative children born to HIV positive mothers (HIV exposed) and HIV negative children born to uninfected

mothers (HIV unexposed) [48]. Tests were done at 6, 12, 18 and 24 months of age. The HIV positive children had a higher frequency of abnormal neurodevelopmental assessments than the control groups at 6 months (16 vs. 3.3, p=0.0001), 12 (31 vs. 7.7, p=0.0001), 18 (40 vs. 7.9, p=0.0001) and 24 (15 vs. 2.2, p=00001). Gross motor was the most affected area which had significantly poorer scores at all the three time points. The HIV exposed and unexposed groups did not differ in any of the neurodevelopmental areas tested. No risk factors for abnormal neurodevelopmental assessment were identified though the frequency of an abnormal assessment was much higher in children with clinical AIDS (ranging from 22 % to 87.5 % at the four time points).

A study by Boivin et al. in Zaire (now Democratic Republic of Congo) assessed two groups of children for cognition [10]. In the first sub-study among children below 2 years, 14 perinatally infected children were compared to 20 exposed and 16 unexposed children on tests of gross motor, fine motor, language and personal-social skills. Testing was done at 3, 6, 9, 12 and 18 months of age. Repeated measures analysis of variance showed the HIV group had poorer gross motor, fine motor and personal-social skills than the other groups. Similar to the previous study by Msellati and colleagues [48], there were no differences in outcome between the exposed and unexposed groups. In the second sub-study with children over 2 years of age, 11 children perinatally infected were compared to 15 exposed and 15 unexposed children on tests of cognition, language, motor, sequential processing, simultaneous processing, nonverbal reasoning and mental processing composite. The HIV infected group had poorer scores in motor, sequential processing, simultaneous processing, nonverbal reasoning and mental processing composite. Contrary to the earlier studies above, the exposed group performed poorer on many of the neurodevelopmental outcomes compared to the unexposed group.

Drotar and colleagues [21] carried out a larger study in Ugandan children using the same groupings from the above two studies (infected, exposed and unexposed) [21]. Seventy nine HIV infected children were followed up from birth and compared to 241 exposed and 116 unexposed children on tests of mental development, motor and information processing. Testing for mental development and motor was done at 6, 9, 12, 18 and 24 months while information processing was assessed at 6, 9 and 12 months. A test score was categorised as impaired if it was more than two standard deviations below the mean of the unexposed group. The HIV infected group had more children with impaired motor scores at all the five time points and more children with impaired mental development at 6 and 18 months only. There were no differences in information processing scores between the three groups. No risk factors for motor and mental development deficits were identified.

In a follow study of the Drotar et al. [21] cohort 6 years later, Bagenda et al. assessed cognition (Sequential Processing and Simultaneous Processing) and academic achievement (Reading, Spelling and Arithmetic) in 28 HIV infected, 42 exposed and 37 unexposed children [2]. The HIV exposed group had higher scores than the HIV infected group in the Sequential Processing measure of Hand Movements (8.1 vs. 10.4, p=0.02) and in the academic achievement measure of Reading (62.1 vs. 73.2, p=0.009). There were no other differences in simultaneous and sequential processing subscales and in reading, writing and arithmetic between

the groups. The authors concluded that the high mortality in the HIV infected group may have selected children who had more CNS involvement leaving behind children that have average cognition functioning. However other factors that differed between the groups were not controlled like the anthropometric results. Secondly, being a school going age, education exposure was not factored in the analyses. These factors are associated with cognitive functioning in Ugandan children of the same age range [4].

Ruel and colleagues [54] conducted a study that addressed some of the limitations in the above studies when they assessed cognition in HIV infected Ugandan children who had high CD4 counts thus ineligible for ART [54]. They examined the effect of HIV, including clinical stage, on cognition and controlled for other socioeconomic variables that may affect cognition like age, sex, socioeconomic status and quality of the home environment. HIV infected children had poorer reaction time, general cognition, working memory, visuospatial processing, reasoning and motor scores than a control group of HIV negative children. When children in clinical stages 1 and 2 were compared to controls, only visuospatial processing, reasoning and motor skills were impaired implying most deficits were in those in stage 3. Another study found that in this group of HIV infected children, those having subtype A had poorer performance in working memory and visuospatial skills than those with subtype D [13]. The conclusion from this study is that HIV infected children who are asymptomatic are already CNS comprised with several cognitive deficits that may affect other functional areas, with subtype A more at risk of these deficits. ART initiation may therefore be needed earlier and may need to consider drugs with greater CNS penetration for those with subtype A. The effect of time of infection (peri- or post-natal) was not assessed in this study.

In an attempt to study the association between time of infection and neurodevelopmental outcome, McGrath et al. assessed mental development and psychomotor development in HIV infected Tanzanian children at 6, 12 and 18 months of age and compared them to HIV negative children [47]. Children infected with HIV were categorised as infected within the first 21 days or after 21 days. Children infected within the first 21 days had lower mental and motor performance than the controls at all time points while those infected after 21 days also had poorer performance but not significantly for mental performance at 6 and 18 months. Motor performance had higher mean differences than mental performance for all time points in both HIV groups. Testing HIV positive at birth was associated with a 14.9 times higher risk of being delayed in mental development while testing positive after birth was associated with a 3.2 times higher risk than the HIV negative children. Children already infected at birth are thus more likely to have poorer neurodevelopmental outcome than those infected later. The authors concluded that early infection could interfere with the myelination process affecting projection fibres and association and commissural connections resulting in global deficits including motor abnormalities. Later interference with myelination could affect commissural connections and connection with the poles of the cerebral lobes affecting cognitive functions.

Further insight into the pathogenesis of these cognitive deficits in asymptomatic HIV infected children is from imaging studies. Hoare et al. assessed neuropsychological performance and diffusion tensor images in 12 highly active antiretroviral therapy (HAART) naive HIV infected children. Similar assessments were done in 12 controls matched for age, gender and race. HIV infected children had poorer neuropsychological test performance in general intelligence, motor functioning, processing speed, visuospatial processing, memory and executive function. In the HIV groups, there was decreased fractional anisotropy and increased radial diffusivity in the corpus callosum, increased radial diffusivity and mean diffusivity in the superior longitudinal fasciculus. These imagining findings are indicative of white matter damage and myelin loss in the corpus callosum and superior longitudinal fasciculus [30]. Poor test performance correlated with imaging abnormalities in the corpus callosum and superior longitudinal fasciculus. This study shows that damage to the white matter and demyelination are important factors in the pathogenesis of cognitive deficits in HIV infected children.

Cognitive Outcomes of HIV Infection in HAART Exposed Children

There are clear benefits of HAART treatment on cognitive functioning in African children. Van Rie et al. [56] assessed cognition in 35 HIV infected Congolese children and compared them to 35 exposed and 90 unexposed children [56]. The HIV infected group had more mental and motor developmental delays than the unexposed group (60 % vs 24 %, $p<0.0001$ and 29 % vs 0 %, $p<0.0001$ respectively). The exposed group also had more children with mental and developmental delays than the unexposed group (40 % vs 24 %, $p<0.09$ and 14.3 % vs 0 %, $p<0.0005$ respectively). Compared to the unexposed group, there were more language comprehension and language expression delays in the HIV infected (77 % vs 13 %, $p<0.0001$ and 85 % vs 13 %, $p<0.0001$ respectively) and exposed groups (11 % vs 13 %, $p<0.99$ and 47 % vs 13 %, $p<0.018$ respectively). Contrary to previous studies using the same measures (Bayley Scales of Infant Development), children in this study had motor development less affected than mental development.

When these children were initiated into HIV care (including HAART) and given cognitive testing at 6 and 12 months later, improvement in mental and motor development were observed [57]. Children who presented early for care (at clinical stage 1 or 2) had better motor scores at all time points than those who presented late. Young children ($\leq$29 months) and not older children (>29 months) had an accelerated gain in motor and cognitive scores over the 12 months. This study suggests that HIV care and treatment may improve cognitive development in children especially once initiated early. This study shows the importance of early initiation of HAART given the results in McGrath et al. [30] where children who were infected earlier had poorer cognitive outcomes than those detected much later [47].

Laughton and colleagues assessed the benefits of early versus deferred HAART on cognitive outcome in children [45]. Children were randomly assigned to early HAART (n = 64, given within 3 months) or deferred HAART (n = 26, given when there was clinical or immunological progression to AIDS) and assessed for locomotor, personal-social skills, hearing & language, eye & hand coordination, and performance (fine motor and visuospatial skills) using the Griffiths Mental Development Scales. Two control groups of HIV exposed and unexposed children were also assessed. Children in the early treatment group had better Locomotor scores than the deferred group. The early treatment group also had similar scores to the uninfected control groups for all scores except locomotor where the exposed arm had better scores. The effect of early HAART on cognition compared to the deferred group as well as the comparative performance of the early HAART group to the control groups highlights the importance of early therapy on CNS integrity in HIV infected children.

Interventions to Prevent Cognitive Deficits due to HIV Infection

Primary Prevention

Prevention (or elimination) of mother to child transmission of HIV is one intervention preventing the spread of HIV to children born to HIV infected mothers. However no trials have been conducted to assess cognitive outcomes in children whose mothers received PMTCT and those who did not. Studies comparing cognitive outcome in HIV infected children and HIV negative exposed children (born to HIV infected mothers) do provide evidence that PMTCT could prevent cognitive deficits resulting from HIV infection in young children. Van Rie et al. [56] observed more mental and motor development delays in HIV infected children compared to the exposed children [56]. However earlier studies did not see any differences between the exposed and the HIV infected groups [10, 48]. In one sub-study by Boivin et al. the exposed group had poorer cognitive outcomes than the HIV negative unexposed children [10]. This latter finding suggests that environmental variables like caregiver characteristics may also play a role in determining cognitive functioning in children necessitating interventions targeting them.

Secondary Prevention

For children infected with HIV, early initiation of treatment may delay the progression to severe disease leading to better cognitive outcomes. Studies by Van Rie et al. [57] and Laughton et al. [45] show that children who present to care in the early stages of the disease and those who receive HAART within 3 months have better cognitive outcomes than those who present for treatment later or receive treatment

after 3 months [57, 45]. However HAART alone may not improve cognitive outcome as Jeremy et al. [35] noted necessitating additional interventions [35].

Tertiary Prevention

Like for children surviving severe malaria, computerised cognitive rehabilitation training (CCRT) has also improved cognitive outcome in children infected with HIV. Boivin and colleagues randomized children to either cognitive training or a non intervention arm [12]. Ten sessions of 45 min each were completed in 5 weeks for the intervention arm training memory, attention, visuomotor and reasoning. The intervention group had better outcomes on learning and attention compared to the control group. In recognition of the effect of the care giving environment on cognitive outcome, Boivin and colleagues piloted an intervention aimed at improving the child-caregiver relationship and assessed the cognitive benefits in HIV infected children [15]. The intervention involved a 12 month structured caregiver training that emphasised nurturing children through interacting with the environment in ways that enhance their cognitive development. Children were randomised to either the caregiver training intervention or to a health and nutrition training. Children in the intervention had better visual reception and memory, their mothers were less depressed and they had better interaction with their mothers at the end of the intervention compared to the control group. This caregiver intervention shows promise in improving cognition in children with HIV since it is implemented in the community and does not require specialised equipment like CCRT. A trial is underway in Uganda to look at the long term benefits of this intervention and whether the caregiver training improves cognition in other children in the household.

Conclusion

Malaria infection, from asymptomatic to severe disease is associated with cognitive deficits whose severity increases along the disease spectrum. Clinical features of the disease are associated with cognitive outcome and these should be the focus of adjunct therapies to prevent poor cognition. Unfortunately, trials for adjunct therapies have not been successful while the long benefit of cognitive training interventions in severe malaria survivors is not known. Chemoprevention trials are the best solution at present as they reduce disease burden and also result in better cognitive outcomes in children.

HIV infection is associated with cognitive deficits in African children with motor difficulties being commonly reported. These deficits are associated with white matter loss, demyelination and having subtype A. The effects on cognition may also be an indirect effect through deficient caregiving from the infected mother as seen in poorer test scores in the exposed but negative children. Early initiation of treatment, cognitive training and improving the caregiver-children interaction may improve cognitive outcome.

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