Important HIV-associated conditions in HIV-infected infants and children

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Abstract

This article is the last in a series of 6 articles that discussed the management of HIV-infected children in a clinically orientated, practical and concise fashion. The topics covered previously include; 1) Preventing and diagnosing HIV-infection in infants and children, 2) Initiating anti-retroviral therapy in HIV-infected infants and children, 3) Maintaining HIV-infected infants and children on anti-retroviral therapy, 4) Common opportunistic infection in HIV-infected children: Part 1-respiratory infections and 5) Part 2 non-respiratory infections.

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Introduction

In addition to the morbidity and mortality caused by opportunistic infections that we discussed in the two previous articles, a number other conditions are also associated with HIV-infection. These HIV-associated conditions may have devastating consequences; in this article we discuss some of the most common and severe conditions according to the main system affected.

Neurological conditions

HIV encephalopathy

HIV encephalopathy is the most common neurological manifestation of HIV in children and may be a presenting feature. The diagnosis is mainly made on clinical grounds. Regular measurement and charting of the head circumference in the first 3 years of life and careful assessment of the neuro developmental progress is an important part of the management of all HIV-infected children. Feeding difficulty, especially nasopharyngeal incoordination, may be an important pointer to neurological illness and may lead to other co-morbidities such as malnutrition and/or aspiration with chronic lung disease.

The American Academy of Neurology AIDS Task force defined HIV encephalopathy as:

At least one of the following progressive findings present for at least two months in the absence of a concurrent illness other than HIV-infection that could explain the findings.

1. Acquired microcephaly as demonstrated by head circumference measurement or brain atrophy on serial computed tomography (CT) or magnetic resonance imaging (MRI) imaging in children younger than 2 years of age.
2. Acquired symmetrical motor deficits manifested by two or more of the following: paresis, pathological reflexes, ataxia or gait disturbance.
3. Failure to attain or loss of developmental milestones or loss of intellectual ability verified by standard developmental or neuropsychological tests.

Lumbar puncture (LP) is only required if a central nervous system (CNS) infection is suspected and neuroimaging, although mentioned in the case definition, is not required to establish the diagnosis. Neuroradiological changes usually lag behind clinical findings.

The following features are associated with specific special investigations:

- Cerebrospinal fluid (CSF) - normal or lymphocytic pleocytosis and mildly elevated protein
- CT-Brain - global cerebral atrophy and basal ganglia calcifications
- MRI-Brain - diffuse white matter changes.

HIV related encephalopathy is a WHO Stage IV condition, mandating highly active antiretroviral therapy regardless of the CD4 count or percent.[1-3] Supportive physiotherapy, occupational therapy and speech therapy may be required. It is important to inform caretakers that although some functional improvement should occur, this may not be up to the age related norm. Table 1 illustrates the various clinical courses in the absence of HAART. Timely initiation of HAART will significantly reduce the development of HIV encephalopathy.

HIV-infected children are also at risk of other developmental and neuropsychiatric problems besides HIV encephalopathy. These conditions are summarized in table 2 and should be managed as in HIV-uninfected children; expert help should be sought as indicated.[4]

Seizures

Seizures are not usually associated with HIV related CNS disease, as HIV affects mostly the white matter. However, simple febrile seizures may occur. The indications for lumbar puncture and imaging are as for HIV-uninfected children and if seizures do occur, standard anticonvulsants usually result in satisfactory control. There may be significant drug interactions between anticonvulsants (carbamazepine in particular) and antiretroviral drugs, which may cause drug-

Table I: Various clinical courses described for children with HIV encephalopathy

Type	Course	
Static	Developmental arrest (No loss or gain of milestones)	
Progressive	Acute	Rapid and relentless progression
	Plateau	Indolent, slow progression

Table II: Neurological and behavioural phenomena associated with HIV-infection in children

Area of dysfunction	Age	Features		
Motor	May start at young age	Early	Late	Rare
		Spastic diparesis*	Spastic quadriparesis Pseudobulbar palsy	Dystonia Tremors Ataxia Focal signs
Behavioral	Often detected in older children	Attention deficit hyperactivity disorder		
		Anxiety		
		Oppositional defiant disorder		
		Conduct disorder		
Cognitive	All Ages	Expressive language deficit		
		Learning disabilities		
		Cognitive scores below childhood norm		

*Spastic diparesis - Increased tone and pathological reflexes mainly in the legs

related toxicity and/or reduced efficacy. Most experts recommend that carbamazepine should be avoided in HIV-infected children on anti-retroviral therapy (ARVs), as it may induce leucopenia. Therapeutic drug monitoring should be considered to ensure adequate levels of both the anticonvulsants and ARVs.

Pulmonary conditions

Lung disease in children with HIV may have complex etiology, not only related to infections as previously discussed.[5]

Lymphoid Interstitial Pneumonia

Lymphoid Interstitial Pneumonia (LIP) represents 25 - 40% of the pulmonary disease burden in HIV infected children. The natural history of LIP seems variable and is not fully understood. It was previously seen as a relatively benign manifestation of HIV, but it may have severe consequences such as bronchietasis, cor pulmonale and respiratory failure.

Pulmonary findings suggestive of LIP include persistent coughing and tachypnea, while auscultatory findings are rare in the absence of secondary pneumonia. Extrapulmonary findings are often most helpful to support the diagnosis and include; digital clubbing, generalized lymphadenopathy, hepatosplenomegaly and parotid enlargement. The chest radiograph (CXR) usually shows bilateral reticulonodular interstitial pulmonary infiltrates that persists for more than two months, without response to antibiotics or proof of a potential pathogen such as tuberculosis (TB).[1] The lung periphery is often less affected and hilar adenopathy may be pronounced, but airway compression has not been demonstrated.

Due to the chronicity of the symptoms and the CXR findings it may be challenging to differentiate LIP from intra-thoracic TB or bronchiectasis from another cause. It remains debatable whether LIP should serve as an indication to initiate HAART. Current WHO guidelines recommend a CD4-based approach, but it is the belief of the authors that children with LIP together with recurrent pneumonia and/or signs of progressive illness should receive HAART regardless of their CD4 count.[3] Highly active antiretroviral therapy (HAART) is the mainstay of treatment. Corticosteroids may be used to alleviate severe hypoxia, but this should be used with caution and only in severe cases due to considerable side-effects.

Bronchietasis

Bronchiectasis represents an abnormal and irreversible dilatation of the airways that disrupts normal airway functioning and usually results from severe and/or recurrent infections. It is a common problem and occurs in up to 16% of children with HIV. HIV-infected children are vulnerable to develop bronchiectasis for a number of reasons: 1) recurrent and/or severe pulmonary infections resulting from impaired cellular and humoral immunity, as well as compromised local defence mechanisms, 2) LIP and 3) neurodevelopmental abnormalities or oesophagitis that may lead to repeated aspiration.

Productive cough is a common symptom. Classically the production of copious amounts of purulent sputum is described, but young children frequently swallow their sputum, making this a less obvious symptom. Coughing is often worse at night, while other classical signs include clubbing and halitosis. Auscultation findings are nonspecific with crepitations and/or wheezes. The CXR may show a honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, usually with fibrosis and volume loss. A CT scan of the lung is the best diagnostic modality to delineate the full extent of involvement. Treatment includes home physiotherapy and aggressive management of infection. It is the opinion of the authors that all children with bronchiectasis should receive HAART regardless of the CD4% and surgical removal of an affected lobe or segment should be considered if symptoms persist despite good HIV control.[3]

Renal disease

Children with HIV are at risk of developing all the usual renal problems associated with this population including but not limited to acute renal failure due to dehydration and hemolytic uremic syndrome, in addition many drugs including co-trimoxasole may be nephrotoxic.

Glomerulopathy

The incidence of glomerulopathy in HIV-infected children in South Africa is uncertain. Although very few present with frank nephrotic syndrome, an audit at the Red Cross Children's Hospital found that approximately 15% of pediatric patients screened had significant asymptomatic proteinuria. (Personal communication Dr McCullough, Dr Nourse).This is similar to the limited reports from other countries.

In South African children with renal disease who have undergone biopsy typical HIV associated glomerulopathy (HIVAN) was not found to be the predominant lesion rather immune complex disease, as well as a wide range of other lesions. (Personal communication Dr

Nourse) In the era of HAART HIVAN and other HIV associated glomerulopathies may become a more important clinical problem.

Screening with dipstix should be performed every 6 months and if protein or hematuria are detected blood pressure should be determined. Remember that the urine dipstix may be positive without necessarily indicating renal disease when fever, intercurrent infections and and/or nappy rash are present.

The child should be assessed for edema. In the absence of additional clinical features children should be managed according to the algorithm in figure 1. Calculating the protein (mg/dL) creatinine (mg/dL) ratio in a random urine specimen have been shown to have a high correlation with protein excretion determinations. Ratios less than 0.5 in children younger than 2 yr of age and less than 0.2 in children 2 yr of age or older suggest normal protein excretion. A ratio greater than 3 indicates nephrotic-range proteinuria.

Normal creatinine values are age-dependant. The formula for calculating glomerular filtration rate and the age related normal values are given in table 3.

These children should be managed with support from a pediatric nephrologist or experienced pediatrician.[6-8]
Management guidelines include the following:

- HAART prevents the onset, may slow the progression and even induce remission. All patients with proven glomerulopathies and those with proteinuria should receive HAART. Unfortunately glomerulopathies other than HIVAN may have a less favorable response. In children with established renal failure the dosages of drugs needs to be adopted according to the glomerular filtration rate.
- ACE inhibitors should be started in children with more than 1g/l of proteinuria. Caution should be exercised in children with suspected salt-losing nephropathy. Discontinue temporarily in the presence of dehydrating diarrhea as acute tubular necrosis may be precipitated. As these drugs may be teratogenic girls of child-bearing age should use birth control.
- Corticosteroids and cyclosporin may benefit some children but should not be used without expert advice.

Urinary tract infections

Like in HIV-negative children clinicians should suspect urinary tract infection in any child with a febrile illness with out a detectable focus of infection. The management of these patients are similar to HIV-negative children. Children <1yr of age with a confirmed urinary tract infection should be investigated with a renal ultrasound and a micturating cystogram. Children >1 year should have a renal ultrasound and further investigations should be tailored according to the findings.

Figure 1: Assessment of proteinuria

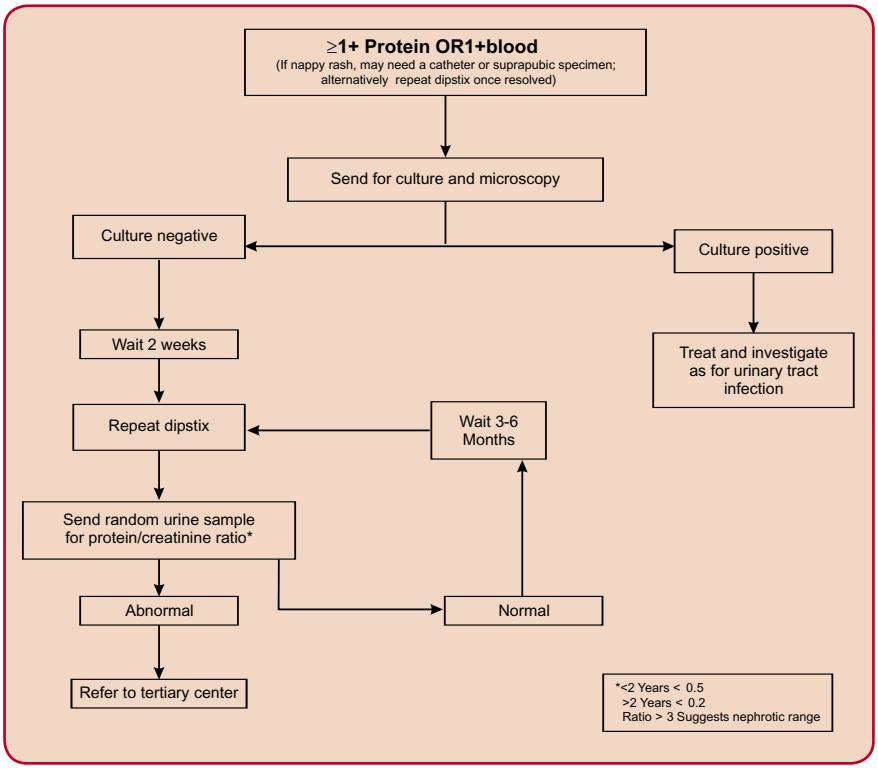

Table 3: Schwartz formula and age related normal value of creatinine and glomerular filtration rate

Normal age related serum Creatinine (µmol/L)	
Infant	1835
Child	2762
Adolescent	4488
Schwartz formula : GFR (µmol/L)=k x height (cm) x Creatinine (µmol/L)	
Preterm Infant	k=29
Infants < 1 year	k=40
Children 1-13 years	k=49

Cardiac conditions

Cardiomyopathy

The new WHO clinical staging classifies dilated cardiomiopathy as a stage 4 disease, due to the high morbidity and mortality associated with this condition. Management includes standard antifailure therapy, such as diuretics and low dose ACE inhibitors; digoxin is rarely indicated. Because it is recognized as a stage 4 disease, initiation of antiretroviral therapy is indicated regardless of the CD4 count.

Cor pulmonale

Right heart failure may occur as a result of chronic lung disease or airway obstruction. The diagnosis is mainly made on clinical grounds with signs of right ventricular hypertrophy. If available, CXR, ECG and/or echocardiography findings may provide confirmation. Management includes treating the underlying cause if possible and providing optimal supportive care.

Conditions of the gastro intestinal tract

HIV associated failure to thrive

Failure of an HIV-infected child to gain weight may have multiple causes. Poor food security, poor nutrition choices and infections of the gastrointestinal tract or chronic diseases such as TB may all contribute. Gastrointestinal infec-

tions may lead to anorexia, dysphagia, malabsorption and/or protein losing enteropathy. An attempt should be made to make a definitive diagnosis and to address the underlying problem as growth failure is an important component of the staging process.[1] In addition to the contribution of opportunistic infections, HIV-infection itself may cause loss of appetite, malabsorption and an increased metabolic rate.

A good history should be taken focusing on the diet, swallowing disorders, other intestinal complaints (diarrhoea and abdominal pain), and symptoms of systemic disease. The dietary history should include details of the type, frequency, and amount of food the infant receives. Weight, length, weight for length, and growth rate should be evaluated. A full clinical assessment should be performed and special investigations requested as indicated.

All children should be dewormed regularly (every 6 months), while food security and the need for supplementation should be assessed. If significant growth failure persists despite regular deworming, the provision of adequate food and additional supplements as needed (especially iron), and after chronic diseases such as TB have been excluded; then HAART initiation should be considered.

Swallowing disorders and reflux

The prevalence of swallowing disorders and gastro-oesophageal reflux disease (GORD) among HIV-infected children is poorly quantified, but is frequently encountered in clinical practice. Swallowing disorders may contribute significantly to morbidity in HIV-infected infants. Coughing and/or milk pouring through the nose whilst feeding is suggestive of poorly coordinated swallowing, which is a particular problem in children with encephalopathy. GORD may be indicated by a history of regurgitating small quantities of feed and/or coughing that follows soon after a feed.

The diagnosis of GORD and its associated complications remains challenging. Oesophagoscopy with biopsy is the investigation of choice to establish a definitive diagnosis of oesophagitis, but this is rarely available. A barium swallow may show irregularity of the oesophageal mucosa or even strictures in the presence of oesophagitis, while active swallowing may be evaluated simultaneously. A therapeutic trial with proton pump inhibitors, trans-pyloric feeds and/or careful observation of the patient while feeding may be required to establish a diagnosis with some confidence.

Omeprazole is the treatment of choice for reflux oesophagitis and acid related upper and lower airway disease.9 However, many airway complications are not acid related; the value of proton pump blockers in the management of these is uncertain and stomach acid fulfills an important protective function against common gastro-intestinal pathogens. Conservative measures such as avoiding feeds of excessive volume, correct feeding technique and positioning of the infant during and after feeds are often useful. Children with persistent severe symptoms not responding to conservative measures and/or medical therapy should be evaluated for a surgical anti-reflux procedure.

Uncoordinated swallowing is even more challenging to manage. The assistance of a speech therapist is invaluable in this situation. Strategies such as manipulating the consistency of feeds and appropriate feeding technique frequently control the symptoms. Some children may require naso-gastric feeding by tube (infants with respiratory distress should receive an oro-gastric tube), but this should only be considered for short term management or in severe cases. The infant's caretakers should be counseled and assisted with switching to solid food safely and with the use of cup feeds. In very severe cases, where no progress is made, a gastrostomy may be the only long term option. When this condition is due to HIV-associated neurodevelopmental delay then HAART may improve the problem.

Haematological conditions

Hematological abnormalities are common in HIV-infected children. When more that one cell type is persistently affected a formal bone marrow biopsy is indicated.

Thrombocytopenia

HIV-associated immune thrombocytopenia is also fairly common and may be problematic to treat. Children with platelet counts > 30 000 µl/microL seldom have serious bleeds. Like with other forms of idiopathic thrombocytomenic purpera the management is much discussed. Although the use of corticosteroid and/or intravenous immunoglobulin (IVIG) is widely advocated, these modalities have not been studied in a controlled fashion. Various doses and durations of treatment are mentioned in the literature. In situations where a rapid increase of the platelet count is desirable (ie acute severe bleeding) IVIG may have an advantage over steroids.[10] Prolonged courses of steroids in children that show no response should not be given. Recurrent severe bleeding is an indication to initiate HAART, regardless of the CD4 count.[3]

Anemia

Anemia is extremely common, but before ascribing the anemia to HIV, common causes such as malnutrition, iron deficiency and chronic infections should be excluded. In addition antiretroviral drugs, zidovudine (AZT) in particular, may cause anemia. A positive Coombs test reflects the presence of immune mediated haemolysis, this may have many causes for example various viral or bacterial infections, the use of antibiotics or other drugs and it may also be a HIV related phenomenon.

Conclusion

This article is the last in our series of 6 articles that discussed the management of HIV-infected children. The full series is available on-line at SAFP website (www.safpj.co.za) and should assist clinicians to provide optimal care to HIV-infected infants and children

The second edition of the Southern African Handbook of HIV medicine is currently under review and clinicians are encouraged to consult this as a supplementary text. Thank you for caring about HIV-infected children, we trust that you will find it as interesting, frustrating and rewarding as we do.

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