

Viral Causes of Diarrhea in Children in Africa: A Literature Review

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Abstract

Childhood diarrhea remains one of the most important health issues worldwide with high morbidity and mortality rates majorly in Africa and other developing countries. Several etiological agents have been linked to acute diarrhea in children. Rotavirus has been the major cause of viral childhood diarrhea in Africa however, with the introduction of national vaccine program in several endemic countries; there seem to be a decline with other viruses including norovirus, adenovirus, astrovirus and parvovirus emerging as key agents in childhood diarrhea in Africa. Hence the need for appraisal to have an update on rotavirus as the main player and to identify the position of other viral agents in the disease burden, which will provide useful information for further study and intervention. Literature search was carried out using search words such as “viral etiology of diarrhea”, ‘epidemiology’, ‘pathogenesis’, ‘treatment/management’ of childhood diarrhea in Africa in PubMed and Google Scholar. Relevant articles were selected. Literature reveals that rotavirus remains the major causative agent of viral diarrhea in African children. High mortality and morbidity rate is on the decline as a result of the inclusion of rotavirus vaccine in most African countries’ national immunization programs.

Keywords: Diarrhea; Rotavirus; Dehydration; Norovirus; Viral; Africa

Introduction

Diarrheal disease is a leading cause of child morbidity and mortality globally [1]. It has been reported that a high proportion of deaths as a result of diarrhea occurs in children under the age of five years [2]. Diarrhea is defined as having loose or watery stools at least three times per day, or more frequently than normal for an individual. Most episodes of childhood diarrhea are mild, acute cases can lead to significant fluid loss and dehydration, which may result in death or other severe consequences if fluids are not replaced at the first sign of diarrhea [3]. Though the burden of diarrheal disease worldwide is high, developing countries such as countries in Africa account for over two million deaths of young children per year [4]. Viral agents tend to be the major etiology of diarrheal disease in Africa [5]. Viruses such as Rotavirus, Norovirus, enteric Adenovirus and Parvovirus have been implicated in diarrheal disease with rotavirus being a leading cause of the disease [6,7]. Viral gastroenteritis is highly contagious hence it is easily transmitted through contaminated food or water [3]. Google Scholar and PubMed databases were queried for relevant articles using the search words such as “viral etiology of diarrhea”, ‘epidemiology’, ‘pathogenesis’, ‘treatment/management’ of childhood diarrhea in Africa. Articles were selected for further evaluation based on the following inclusion criteria: (i) Studies carried out in Africa, (ii) Publications between 2000 and 2017. Two hundred and forty three (243) articles were retrieved of which 172 articles were excluded since they did not meet the inclusion criteria for articles to be reviewed. Some of the excluded articles were studies that researched bacterial and viral causes of diarrhea but were passive on the viral causes of the disease. Seventy-one articles

were reviewed with two articles published before year 2000 because of their relevance to this discuss. Articles were analyzed and findings organized according to, rotavirus childhood diarrhea in Africa, epidemiology, pathogenesis, clinical manifestation, diagnosis, management/control, noroviruses and other viral agents and childhood diarrhea in Africa.

Rotavirus

Rotavirus Childhood Diarrhea in Africa

Rotavirus is the major cause of infant and childhood diarrhea in Africa. It has been estimated that rotavirus causes approximately 453,000 deaths per year, mostly in countries of Africa and Asia [8]. Rotaviruses are classified into sero-groups A–G and at least 4 subgroups (SGI, SGII, SGI + II and SG non-I/non-II) within group A have been recognized. Rotavirus A, the most common cause of severe diarrhea in children globally occurs in five major VP7 and VP4 (P) genotype combinations comprising G1P[8], G3P[3], G4P[8] and G9P[8]. Although G8 a common bovine rotavirus genotype has been frequently reported among children in Africa [9–11]. Diarrhea caused by rotavirus is of great importance because of some factors including:

- The ubiquitous distribution of rotavirus strains in nature
- The increasing number of unusual and novel rotavirus G and P genotypes detected in humans
- The considerable antigenic diversity of rotavirus strains
- Their wide host range
- Their complex pathogenesis
- The complicated epidemiological chain involving animal, human and the environment [12].

In Nigeria 30,800 deaths of children < 5 years old is attributed to rotaviruses which accounted for 14% of all deaths attributed to rotavirus in 2013 [13]. Junaid et al. [14] reported detection of rotavirus in the feces 22(13%) of children with acute diarrhea, 90.9% of positive cases were children under two years of age with highest prevalence in children 7–12 months of age attending Jos University Teaching Hospital Nigeria. Also Iyoha and Abiodun [15] reported rotavirus of varying genotypes as the cause of acute watery diarrhea among children less than five years in Benin City Nigeria. Alkali et al. [16] reported rotavirus infection in 51 of 200 children < 5 years of age having diarrhea in Sokoto state Nigeria putting prevalence of the disease at 25.5% in the state. In a similar study in Zaria, North central Nigeria, Grace and Jerald [9], reported 15.6% prevalence of rotavirus infection among diarrheic children with the peak of infection occurring between 1–6 months of age. Uzoma et al. [17] also reported 37.1% of rotavirus positive cases in children less than five years of age with diarrhea at a Federal Medical Centre in Asaba Delta State Nigeria. Three rotavirus genotypes were common which were G3P [6], G1P [6] and G12P [8].

Second to Nigeria in deaths attributed to rotavirus infection in children < 5 years in the 2013 survey is the Democratic Republic of Congo (DRC) with 13,526 deaths resulting in 6% of global death [13]. A study carried out in 2012 by Sangaji et al. [18] in Lubumbashi DRC showed that out of 193 cases of acute diarrhea, 104 (53.8%) infants were infected with rotavirus. Surveillance of the outbreaks of acute gastroenteritis in 2003, 2004 and 2005 in Kinshasa, Democratic Republic of Congo showed that group A rotavirus was detected in 195 (76%) of infected children < 5 years of age [19]. In rotavirus surveillance in Kisangani, DRC it was revealed that the diversity of 99 rotaviruses detected between 2007 and 2010, were predominantly G1 of G-type and P [6] of P-type. A total of eight different G/P combinations were found, which were G1P [8], G8P [6], G2P [4], G12P[6], G1P[6], G9P[8], G4P[6] and G8P[4] [20].

Another study by Tate et al. [13] recorded 9,682 deaths and 6,817 deaths respectively due to rotaviruses in 2013 from Angola and Ethiopia. G3P [6], G1P [8] and G2P [4] are common strains of rotaviruses found in Ethiopia [21]. In rural Southern Ethiopia it was reported that 43.6% of children less than five years of age had diarrhea as a result of rotavirus [22]. From September 2012 through December 2013, 344 stool samples were collected from children younger than five years in Bengo, Angola to determine the etiology of diarrhea, 25.1% rotavirus was detected as the cause of diarrhea only second to *Cryptosporidium* spp. [23].

In Gabon, between March 2010 and June 2011 Lekana-Douki et al. [24] reported rotavirus as the most frequently detected enteric viruses in children under five years of age. In a study carried out in Abidjan Cote d'Ivoire, Akranet al. [25] did a molecular characterization and genotyping of human rotavirus strains recovered from infants and young children with acute diarrhea. It was reported that VP7 genotype G1 strains were the most common circulating strains during the study period. In a related study two human genotypes G10 rotavirus strains 3008CM and 1784/CI/1999 were isolated in Cameroon and Cote d'Ivoire during the 1999–2000 rotavirus season. Comparison of nucleotide and amino acid sequences coupled with phylogenetic analyses of the G10 strains showed that the strains were closely related to the human G10 strains that were detected during the 2001–2003 rotavirus season in Ghana.

Epidemiology

The burden of rotavirus disease is high in Africa. The virus commonly causes diarrhea in children between the ages 6–24 months, however children at younger ages come down with severe infection although neonatal infection is probably nosocomial and tends to be mild. This early protection has been attributed to trans-placental antibodies that persist in the infants soon after birth. Transmission of human rotavirus is by direct person-person contact. It is also presumed to be transmitted through the fecal-oral route and contact with contaminated environmental surfaces. Thus the virus can persist on toys and hard surfaces in daycare centers indicating that fomites may serve as mechanism of transmission [26–28]. Since the virus is ubiquitous, its ability to cause disease in young children is independent of socioeconomic class, hence improvement in public health measures, such as in developed countries does not affect morbidity. Thus morbidity in Africa equals morbidity in high-income countries. However approximately 45% of child mortality due to rotavirus infection occurs in Africa [29]. The vast majority of rotavirus disease is caused by group A rotavirus, although mixed infections tend to be common in Africa. Occurrence of rotavirus infection is also seasonal. Armah et al. [30] reported the seasonality of rotavirus infection in Ghana. Infection was high during cool dry months and low during the wet season. Peaks of infection were recorded in February (26.2%) and

September (24.5%). In Guinea-Bissau West Africa, Fischer et al. [31] reported a seasonal pattern of rotavirus infection with annual epidemics occurring during the relatively dry and cooler months from January to April. In a similar study Akoua-Koffi et al. [32] reported the highest percentage of rotavirus cases in the republic of Ivory Coast observed in January 2008. In Libya it was estimated that the incidence range of 418–557 rotavirus hospitalizations per 100,000 children < 5 years of age occurred between August 2012 and April 2013. Most (86%) rotavirus cases were below two years of age with distinct seasonal peaks in winter (December–March) months [33].

Pathogenesis

The virus enters cells by receptor-mediated endocytosis and forms a vesicle known as an endosome [34]. Replication of rotaviruses takes place exclusively in the differentiated epithelial cells at the tips of the villi of the small intestine. New virus is produced after 10–12 hours. Progeny viruses are then released in copious numbers into the intestinal lumen ready to infect other cells. Cellular damage results in the reduction of absorptive surface thus leading to impaired absorption of nutrients, electrolytes and water. NSP4 a rotavirus protein encoded by RNA segment 10 results in the production of viral enterotoxin. Rotavirus infection is followed by a local humoral and cell-mediated immune response and is normally overcome within a week [35,36].

Clinical Manifestation

The clinical manifestations of rotavirus infection are nonspecific and similar to those caused by other gastrointestinal pathogens, although they tend to be more severe. The onset of rotavirus illness begins with acute fever with temperature elevating over 102°F and vomiting followed by watery diarrhea which lasts for 2–6 days. Clinical symptoms can range from mild to very severe depending on the rotavirus strain and also it can be life-threatening if children are already malnourished [29,35,37]. Diarrhea coupled with vomiting can promptly result in dehydration in infants and young children. Dehydration is characterized by thirst, lethargy, dry mouth, restlessness, dry skins, sunken eyes, reduced frequency of urination and extreme sleepiness. Dehydration is a serious complication of rotavirus, if not checked immediately can lead to hypovolemia [14]. Parisi et al. [38], reported a rare gastrointestinal complication “Protein-Losing Enteropathy (PLE)” which is characterized by intestinal loss of protein with consequent hypoproteinemia and generalized edema in an infant with rotavirus infection.

Diagnosis

Latex agglutination assay, enzyme immunoassay and immunochromatographic tests have been employed in the diagnosis of rotavirus infection. These tests are fast, easy to perform and are highly sensitive [39,40]. However, the use of Polymerase Chain Reaction (PCR) methods has also been extensively used in the diagnosis of rotavirus and other gastrointestinal viral infections. These PCR methods have proven to have their own advantages over conventional methods mainly due to a higher analytical sensitivity. Leva et al. [41] demonstrated the diagnostic performance of Luminex xtag gastrointestinal pathogens panel to detect rotavirus in Ghanaian children with and without diarrhea. Electron microscopy is also applied in the detection of rotaviral particles in stool.

Management/Control

Rotavirus infection has no specific antiviral therapy hence treatment is supportive. Oral and sometimes intravenous (those with severe diarrhea) rehydration should be given to replenish

host fluid and electrolytes. Nutritional therapy should also be considered which could help reduce morbidity and mortality resulting from rotavirus infection [39,42,43]. In Africa low standard of living and poor hygiene may exacerbate the cases of rotavirus. Improvement in sanitation and the availability of clean water have not decreased the rate of rotavirus diarrhea in developed countries either therefore vaccination is considered the first strategy in the prevention of rotavirus infection [13]. In 2009 the World Health Organization (WHO) recommended that all countries and in particular those countries with high diarrhea mortality rates in children, should introduce rotavirus vaccines into their national immunization program. By the end of 2014, more than 70 countries had introduced rotavirus vaccine into their routine immunization programs for children [15]. Rotavirus vaccines are an essential and lifesaving intervention which has helped reduced the severity of the disease. There are two internationally licensed vaccines, Rotarix (GlaxoSmithKline Biologicals) and RotaTeq (Merck) which has been introduced and is being used in the expanded programs on immunization (EPI) of African counties [29]. In Ghana rotavirus vaccine was introduced in 2012 and this resulted in the reduction of hospital admissions positive for rotavirus from 48% in the pre-vaccine period to 28% post-vaccination among < 5years olds [44]. In a similar evaluation in Malawi where the monovalent rotavirus vaccine was also introduced in 2012, there was reduction in the disease burden in infant < 12 months but not in older children [45]. There was significant reduction in acute gastroenteritis associated in hospital mortality and morbidity following ROTARIX introduction in Zambia. The greatest reduction was seen in infant < 1year which accounted for 84.4% of rotavirus hospitalization prior to vaccine introduction [46]. This trend of decline in the burden of the disease has also been reported in Togo, South Africa and Botswana [47].

Noroviruses

Second to rotavirus as a cause of childhood diarrhea worldwide is norovirus. There has been an estimated 1.1 million hospitalizations and up to 218,000 deaths in children < 3 years of age annually [48]. Norovirus are members of the *Caliciviridae* family. They are non-enveloped single stranded RNA virus which is genetically diverse with at least 25 genotypes predominantly from genogroup I (GI) and genogroup II (GII). Norovirus strains are classified into seven genogroups (G) based on the analysis of the complete amino acid sequence of the capsid protein. GI, GII and GIV are associated with diseases in humans and within each genogroup there are multiple genotypes [49–51]. Norovirus infections are typically acute and self-limiting. However, the disease can be much more severe and prolonged in infants, elderly and immunocompromised individuals. Outbreaks frequently occur in semi-closed communities such as nursing homes, military settings, schools, hospitals, daycares, cruise ships and disaster relief situations. The virus is highly contagious and extremely stable in the environment, resistant to common disinfectants and associated with debilitating illness [52]. Acute norovirus infection is characterized by non-specific symptoms such as vomiting, nausea, abdominal cramps, myalgias and intense watery non-bloody diarrhea that commonly resolve in 2–3 days. However this can be prolonged in children. Consequences of prolonged norovirus associated gastroenteritis may include irritable bowel syndrome, necrotizing enterocolitis, convulsions and encephalopathy [53]. Transmission of norovirus is via the fecal-oral route. Indirect evidence in epidemiological studies suggests that the virus transmission can be airborne such as explosive vomiting occurring during the disease. Transmission can also occur via water reservoir when ground water is contaminated. Norovirus outbreaks have long been reported to exhibit strong seasonality most often occurring during cold, dry months [54,55].

Norovirus is a common pathogen in children in Africa, with considerable carriage in asymptomatic children [51]. However the burden of norovirus-associated diarrheal infections in the pre and post rotavirus vaccination era has not been fully characterized in Africa [56]. From June 2007 to October 2008 in western Kenya, Shioda et al. [57] carried out a population -based incidence rate of diarrheal diseases associated with norovirus and other viruses. Their study revealed that 2.8–3.3 million cases of norovirus diarrhea occur in Kenya yearly. In a study carried out in South Africa between 2009 and 2013, it was reported that GII.4 variant was predominant in children (≤ 5 years) hospitalized with gastroenteritis [53]. Norovirus was detected frequently from stool samples of children < 5 years of age presenting with diarrhea in Zambia. It was observed that out of 43 isolates that were available for sequencing 31(72.1%) were geno group II (GII) and 12(27.9%) were geno group I (GI) [56]. Between 1999 and 2007 Trainor et al. [58] reported the detection of 11.3% norovirus in 1,941 stool samples obtained from children admitted to hospital with acute diarrhea in Blantyre Malawi. Currently there are no licensed therapeutic intervention measures either in terms of vaccines or drugs available for these highly contagious human pathogens. Genetic and antigenic diversity of these viruses, rapid emergence of new strains, and their ability to infect a broad population by using polymorphic histo-blood group antigens for cell attachment, pose significant challenges for the development of effective antiviral agents [59]. However Takeda Vaccines is developing a candidate NoV vaccine formulation based on adjuvanted virus-like particles from the GI.1 genotype and a consensus GII.4 sequence derived from three natural GII.4 variants. Early clinical trial results have shown good tolerability and robust immune responses to both components. This approach is designed to induce broad protective immune responses in adults and children [60]. In severe diarrhoeal cases supportive treatment can be employed with oral or intravenous rehydration. Also sanitation and health education can be expected to have substantial impact on childhood morbidity [61].

Other Viral Agents and Childhood Diarrhoea in Africa

Adenoviruses belong to the family Adenoviridae and genus Mastadenovirus. To date there are over 60 types of adenoviruses identified, grouped into seven species A to G on the basis of their resistance to neutralization by antisera to other known human adenoviruses or genome analysis. The disease pattern of adenoviruses varies according to species. Adenovirus species F, types 40 and 41, has been found to be regularly associated with gastroenteritis and they are referred to as enteric adenoviruses. These two types are responsible for 1–20% cases of diarrhea, especially in young children, both in developed and developing countries [62]. Adenovirus was identified as one of the viral pathogens responsible for diarrheal diseases in Khartoum State, Sudan. Sixteen percent of cases were attributed to adenoviruses. Diarrheal disease here was linked to poor hygiene since it was evident that most patients drank untreated water obtained from donkey cart source and they had no access to latrines [63]. In a similar study in the region of greater Cairo Egypt, Kamel et al. [64] reported the predominance and circulation of enteric viruses between March 2006 and February 2007. It was observed that there was a 10.4% occurrence of adenovirus and 1.7% of astrovirus. Astrovirus are small non-enveloped viruses with a characteristic star-like structure whose RNA genomes are 6.4–7.7 Kb in size and contains three ORFs designated ORF1a, 1b, and 2, coding for protease, protease-RdRp fusion, and capsid proteins, respectively. Astrovirus including novel MLB- and VA-clade members are commonly found in pediatric stools in Kenya and The Gambia. The most recently discovered astrovirus, MLB3, is the most prevalent

and most commonly found in stools in The Gambia, while astrovirus MLB1 was associated with diarrhea in Kenya [2]. In a study by Phan et al. [65], feces from Burkina Faso children with unexplained acute gastroenteritis were analyzed by deep sequencing. Results revealed the genome of a highly divergent astrovirus. In Tunisia a divergent parvovirus was detected in the feces of a child (18 months old) with an unexplained diarrhea. The patient showed twice daily liquid and greenish feces over three days with no fever, vomiting or dehydration [65].

Conclusion

From our findings rotavirus remains the major cause of childhood diarrhea in Africa even with the ongoing national vaccine program in several countries. Also other viral agents have been identified as childhood diarrhea agents; however there is paucity of information regarding these agents in several endemic African countries. Since childhood diarrhea caused by viruses is still a major threat to the health and wellbeing of the African child, it is therefore pertinent for government to intensify efforts in extending and expanding its national vaccination program and also creating awareness in rural Africa about the disease through education and campaigns. Furthermore parents should consolidate vaccination of their children with proper nutrition and improved hygiene. Research with emphasis on other viral agents beside rotavirus should be initiated to provide the needed information for alleviating diarrhea disease burden in Africa.

Conflict of Interest

The authors hereby declare that there is no conflict of interest.

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