ACUTE DEHYDRATING CHOLERA IN HOSPITALIZED ADULTS AND CHILDREN- AN OVERVIEW AND COMPARISON OF CLINICAL AND IMMUNOLOGICAL RESPONSES

Fahima Chowdhury1, Ashraful I. Khan1, Jason B. Harris2, Regina C. LaRocque2, Abdullah A. Tarique1, Edward T. Ryan3,4, ASG Faruque1, Firdausi Qadri1 and Stephen B. Calderwood2,3

1International Centre for Diarrhoeal Disease Research Bangladesh, ICDDR,B, Dhaka Bangladesh; 2Department of Medicine, Massachusetts General Hospital, Boston, MA, USA; 3Department of Microbiology and Molecular Genetics, Harvard Medical School, Boston, MA, USA; 4Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, MA, USA

Background: Cholera causes severe diarrhea and if left untreated, can lead to severe dehydration and death. It kills tens of thousands of people worldwide every year, mostly in developing countries. After natural infection by V. cholerae, vigorous antigen specific antibody responses are stimulated, which are considered important for long term protection from further disease. Both adults and children are susceptible to severe disease requiring hospitalization. However, preventive measures such as vaccination strategies have been less satisfactory in children and infants. It is not known why cholera vaccines are less effective in children but this could be due to age related or to nutritional factors. The observation that natural infection confers effective immunity against cholera has led to efforts to develop vaccines that will elicit protective immunity not only in adults but also infants and young children. Hypothesis: Severe dehydrating illness due to V. cholerae O1 in children induces a comparable magnitude and frequency of immune responses as those elicited in adult cholera patients, suggesting that the ability to respond to cholera antigens is not primarily affected by age. Objectives: The antibacterial and antitoxic antibody responses were compared in children and adults at the acute and convalescent phases of disease. Method: We included 276 adults (>12 yrs; median 28 yrs) and 121 children (2-12 yrs; median 6.4 yrs) through the period 2001-2005. Statistical analyses were performed by the use of the c2 test for categorical variables and Mann-Whitney U test for continuous variables. The immune responses were analysed at the acute stage (day 2 study) and at early (day 7) and late convalescent (day 21) phases in patients enrolled in the study. The clinical history, vibriocidal antibody responses, immune responses to the toxin coregulated pilus subunit (TcpA), lipopolysaccaride (LPS) and cholera toxin B subunit (CtxB) were measured in serum, and responses compared between adults and children. Results: Severe dehydration was seen more often in adults than in children (94% vs. 86%, p=0.02). The frequency of diarrheal stools prior to hospitalization was higher in adults (p<0.001), with a longer history of disease since onset (p=0.04). As expected, adults required more intravenous fluid replacement than younger patients (p<0.001). More children were infected with V. cholerae O1 Ogawa than the Inaba serotype (52% vs. 30%, p<0.001). V. cholerae O139 induced cholera was seen more often in adults than children (21% vs. 3%, p<0.001). Retinol deficiency (<20 ug/ml) was observed more often in children than in adults (47% vs. 16%, p<0.001). The magnitude of vibriocidal antibody responses was higher in children at the acute (p=0.001), early and late convalescent stages (p<0.001) than in the adults. More children than adults showed >16 fold increases in vibriocidal antibody responses (81% vs. 67%, p=0.01). The magnitude of CtxB specific IgA and IgG responses were higher in children at early and late convalescent stages (p<0.001, and p=0.01 respectively). More children than adults showed >4 fold increases in CtxB-IgA antibody responses (77% vs. 60%, p=0.002). Interestingly, adults showed a higher magnitude of LPS specific IgA and IgG responses (p<0.001) and responder frequencies (p=0.03, p<0.001 respectively). This was also seen for the magnitude TcpA-IgA responses (p=0.001, p=0.004) at early and late convalescent phases, as well as the frequency of responses for TcpA-IgA and TcpA-IgG (p=0.03, p=0.001 respectively). The magnitude of fecal CtxB-IgA antibody response was higher in children at the early convalescent stage (p<0.001). More children than adults showed >2 fold increases in fecal CtxB IgA antibody responses (73% vs. 46%, p=0.009). In addition, children of household contacts of cholera patients were more deficient in vitamin A than adult contacts (35% vs. 9%, p<0.001). Among them, more children than adults became culture positive for V. cholerae during follow-up (p=0.001), had higher vibriocidal antibody responses (p=0.003), and had higher vibriocidal titers at day 4 of study (p=0.05). Moreover, of rectal swab positive contacts, more children had higher vibriocidal and LPS specific IgA antibody responses than adults (p<0.001). Conclusion: Children with dehydrating cholera demonstrate higher immune responses in vibriocidal and cholera toxin specific antibody responses than adults, showing that children in this population may be able to respond satisfactorily to vaccines. The relatively lower response to LPS and TcpA in children may be an age related factor and/or reflect a lack of previous priming. The LPS and TcpA antigens are believed to be critical for mounting a protective immune response and are targets for inclusion in vaccines. As children elicit poor responses to LPS and TcpA, protection may be short lived in them after both natural infection and vaccination. Nutritional intervention may help to increase these responses and may need to be implemented in children with cholera as well as for vaccine studies.