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Poor folate status: A predictor of persistent diarrhoea in young children?

Manger MS, Taneja S, Strand TA, Ueland PM, Refsum H, Schneede J, Nygård O, Sommerfelt H, Bhandari N. (Institute of Medicine, and Centre for International Health, University of Bergen, Bergen, Norway; All India Institute of Medical Sciences, New Delhi, India; Medical Microbiology, Innlandet Hospital Trust, Lillehammer, Norway; Division of Infectious Disease Control, Norwegian Institute of Public Health, Oslo, Norway; Haukeland University Hospital, Bergen, Norway; Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway; and Department of Pharmacology, University of Oxford, Oxford, UK; Department of Clinical Pharmacology, University of Umea, Umea, Sweden.) Poor folate status predicts persistent diarrhea in 6- to 30-month-old north Indian children. *J Nutr* 2011;**141**:2226–32.

SUMMARY

Data from a primary zinc supplementation trial in an urban slum of Dakshinpuri, New Delhi, were used to perform a cohort analysis to study the association between the status of folate/cobalamin and diarrhoeal morbidity in children. Of the initial 3802 children surveyed, 2482 were included in the trial, which met the sample size requirement. For the current analysis, 2296 children who had results for at least one vitamin parameter were included. At baseline, four parameters were measured—plasma folate, plasma cobalamin, plasma MMA and plasma tHcy—among others, using standardized microbiological assays. The cut-off for deficiency state was taken as less than 25th percentile for folate/cobalamin, and more than 75th percentile for MMA/tHcy. Diarrhoea was defined as more than or equal to three episodes of loose watery stools in a 24-hour period, and recovery as the first day of a 72-hour period without diarrhoea. Acute diarrhoea was for a duration of <7 days, prolonged for 7–13 days, and persistent for ≥14 days. The follow-up was done weekly for 4 months and data collected for the preceding 7 days, i.e. every child was visited 17 times. Each week was denoted as a period. Most baseline characteristics among the low and high folate/cobalamin children were comparable except for age, breastfeeding status and levels of other vitamin parameters.

In a total of 250 310 days of follow-up, there were 4596 child-periods of acute diarrhoea, 633 child-periods of prolonged diarrhoea, and 117 child-periods of persistent diarrhoea. Using generalized

estimating equations (GEE) in stepwise logistic regression manner, the risk factors identified for acute and persistent diarrhoea were younger age, enrolment in the months of February to May, and self-reported diarrhoea 24 hours before inclusion. The protective effect of breastfeeding for persistent diarrhoea was decreased when plasma folate was added to the regression. GEE logistic regression was used to estimate associations between the vitamin parameters and diarrhoea. Acute diarrhoea was significantly associated with only high tHcy level (adjusted OR 1.14; 95% CI 1.04–1.24; $p=0.006$). For prolonged diarrhoea, there was no significant association with any parameter. Persistent diarrhoea was significantly associated with low folate level (adjusted OR 1.77; 95% CI 1.14–2.75; $p=0.010$). There was also interaction between low cobalamin and breastfeeding status for acute diarrhoea; adjusted OR for breastfed children was 1.01 (95% CI 0.92–1.12), whereas in non-breastfed children it was 1.48 (95% CI 1.17–1.87), p value for interaction was 0.003. There was interaction between sex and folate status for persistent diarrhoea; adjusted OR for boys was 2.51 (95% CI 1.47–4.28) whereas in girls it was 1.03 (95% CI 0.53–2.01), p value for interaction was 0.03. Generalized additive models showed a linear relationship between log odds of persistent diarrhoea and folate concentration <20 nm/L in boys.

The biological plausibility given for the association between low folate and persistent diarrhoea is that folate is necessary for regeneration of intestinal epithelial cells and recovery from infection, and hence, its deficiency is associated with severity rather than the incidence of diarrhoea. The authors concluded that poor folate status was an independent predictor of persistent diarrhoea in this cohort of children.

COMMENT

Persistent diarrhoea is an episode of diarrhoea of presumed infectious aetiology, which starts acutely but lasts for >14 days, and excludes chronic or recurrent diarrhoeal disorders such as tropical sprue, gluten-sensitive enteropathy or other hereditary disorders.¹ It is more common in malnourished infants and young children.² The major consequences of persistent diarrhoea are growth faltering, worsening of malnutrition and death during subsequent diarrhoeal or non-diarrhoeal illness.² It has been reported that 3%–20% of acute diarrhoeal episodes in children in developing countries are persistent.³

This study examined an association between folate/cobalamin and diarrhoea in children. However, the analysis was conducted as part of a zinc supplementation trial with its own primary objectives.⁴ Hence, the results need to be viewed with caution. A participation rate <60% raises questions on the representativeness of the study group. Had this been a primary objective, the age group included might have been beyond the 6–30 month range.

Sixty per cent of persistent diarrhoea occurs before 6 months, and 90% below 1 year of age.⁵ The percentile cut-offs are justified due to the lack of well-defined absolute values for deficient status, especially in children.⁶ Since it was stated in an earlier report of this study that poor folate/cobalamin status was very prevalent in this study population, such an analysis based on absolute values might not have been possible. The sample size was large and so the probability of even a small difference being significant is high.

GEE logistic regression was aptly used here as this was a dataset with correlated responses and it seems all important confounders have been adjusted for, including zinc supplementation. Age as a predictor of acute/persistent diarrhoea has an adjusted OR close to null, which is also true for the association between high tHcy and acute diarrhoea. The temporality of association appears to be clear, as exposure was measured before outcome. Reverse causality has been mentioned as another explanation, i.e. before enrolment, a higher disease burden in these children would have led to folate deficiency, and only such children had developed diarrhoea during the study. In this study, data were available on self-reported diarrhoea only for 24 hours before inclusion. Since this was an *a priori* stated secondary objective, the possibility of reverse causality could have been anticipated, and comprehensive information collected on previous diarrhoeal morbidity rather than a 24-hour period. The exposure variables were measured objectively. However, as the outcome was measured as reported by the caregiver, this may have introduced information bias.

A memorandum of the WHO mentions that in northern India, 15% of children aged 0–35 months experienced persistent diarrhoea during one year of surveillance, and the case-fatality rate for such episodes was 14% compared with 0.7% for shorter episodes.¹ In a community-based study the incidence of persistent diarrhoea was found to be 6.3 per 100 child-years with the highest incidence in the age group of 0–11 months.⁷ Up to 40% mortality associated with diarrhoeal disease is reported to be due to prolonged episodes and associated malnutrition.⁵ Persistent diarrhoea alone amounts to 47% of diarrhoeal deaths in India.⁸ The average cost of treatment of persistent diarrhoea was estimated to be US\$ 10 in one study which is higher than that for shorter episodes.⁹

Intestinal mucosal damage and consequent problems with nutrient absorption are common features in all children with persistent diarrhoea, and therefore nutritional management is the cornerstone of treatment.^{10–12} Improvements in nutritional status of infants and children as well as prevention and rational

management of acute diarrhoea are keys to prevention of persistent diarrhoea.¹³ With its vast numbers of malnourished children, persistent diarrhoea shall continue to be an important health problem in India. Any intervention that is implementable at the community level to prevent this condition should be welcome. Though evidence is at yet limited, the results of this study do arouse interest, and warrant further community-based research in this direction in India.

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Mortality and non-alcoholic fatty liver disease: Type of study cohort matters!

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Clinical Research, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; Department of Cardiovascular Epidemiology and Population Genetics, National Center for Cardiovascular Research, Madrid, Spain.) Non-alcoholic fatty liver disease and mortality among US adults: Prospective cohort study. *BMJ* 2011;**343**:d6891 doi: 10.1136/bmj.d6891

SUMMARY

A large population-based cohort study was carried out on the basis of data collected during the NHANES III (Third, National Health and Nutrition Assessment Survey), which was used to find the association