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Enteric protozoa and human potential

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The paper by Ajajampur *et al.* in this issue confirms and extends several previous studies from developing countries which show alarming and robust associations between enteric infections, child growth and neuro-development.¹ Their findings that symptomatic giardiasis and diarrhoea predicted wasting and poor performance on a test of cognition (and perhaps lower 'social quotient') are profoundly important and add to the increasing evidence that early childhood enteric infections have long-term growth and developmental consequences which must be addressed if children are to achieve their full potential.^{2–10}

Indeed, evidence is mounting that intestinal infections might have harmful effects not only on childhood stunting — itself an important predictor of IQ — but also on cognitive development which might be independent of the effect of diarrhoea on malnutrition. In an analysis of IQ data from 184 countries, Eppig *et al.* have recently shown that infectious diseases were the most powerful predictor of mean national IQ, even when temperature, GDP per capita and educational indicators were taken into account.¹¹ Furthermore, although 'nutritional stress' correlated with national IQ, even this correlation was lost when the effects of infectious diseases were removed. Although this analysis did not assess enteric infections or diarrhoea *per se*, their specific suggestion that diarrhoeal diseases may lead infectious diseases in causing lifelong detrimental effects on brain development is strongly supported by original reports from our group over the last decade.^{2–7} As with Ajajampur and colleagues' data on the correlation between wasting and 'social quotients', our data suggest that stunting (height-for-age Z-score ≤ 2 SD below the median) at age 2 years may be a surrogate marker of heavy early childhood diarrhoea burdens and a key predictor of later cognitive development. Further follow-up studies of national HAZ-2, wasting and IQ are needed.

Similar to earlier findings in children with intestinal helminthiasis by Stephenson *et al.* and Nokes *et al.*,^{12–14} we and others have reported that early childhood diarrhoea and *Cryptosporidium* infections have lasting effects on child growth and cognitive development.^{2–5,8,9} Furthermore, similar to the results of Eppig *et al.*, we find that diarrhoea, independent of its significant effects on growth, impairs cognitive development (Pinkerton *et al.*, submitted). Clearly, more studies of the long-term impact of major enteric infections, with or without overt diarrhoea, are urgently needed to assess adequately the magnitude and mechanisms by which these devastating developmental impairments occur.

We and others have identified stunting as one of the best surrogate markers of the deleterious effects of early childhood diarrhoeal illness; the decline in cognitive function is apparent 4–8 years later.^{2,3,5,15} In Ajajampur *et al.*'s study, the lack of significant correlation between cognitive function and stunting when cumulative diarrhoeal episodes (and cryptosporidiosis) were taken into account might be explained by younger age at assessment (3 years). Assessing cognition at such a young age can be difficult and it would be

interesting to see the results if the children were followed to an older age. In addition, more comprehensive cognitive testing might provide a clearer picture.

Complex regional and pathogen-specific brain injury might lead to reductions of certain cognitive domain functions which are difficult to assess without a full cognitive battery of tests at an age older than 3 years. Some cognitive domains may require further maturation of neural circuitry which is better assessed in mid-childhood. The finding by Ajajampur's group that *Giardia* spp. infections are associated with cognitive impairment in children in early life is of special interest. Our group also found a significant association between *Giardia* infections and cognitive impairment, especially in apolipoprotein E4 (APOE4)-negative children but not in APOE4 carriers,^{16–18} showing that it is likely that a genetic component is also involved in this effect of *Giardia* infections on brain development. Finally, the finding by Ajajampur's group that breastfeeding might spare cognitive impairment is also of interest as secretory IgA (SIgA) found in breast-milk might also help reduce *Giardia* infections in the offspring.¹⁹

Limitations of current studies include data from single sites (e.g. India, Peru and Brazil) and a relatively moderate number of children for multivariate analyses. Multi-country studies with long-term intense follow-up of birth cohorts, with complete data on factors hypothesised to be associated with IQ, a battery of tests for different aspects of cognitive function, and community-level data on specific symptomatic and asymptomatic infections will help untangle these complex relationships. The answers to these critical questions cannot come soon enough. Diarrhoea mortality has not fallen in the last 5 years²⁰ and diarrhoea morbidity might be increasing in fast-growing populations. Improved diarrhoea prevention and control are urgently needed to improve this mortality; however, to break this vicious cycle, new research is required as well as strategies to address growth and IQ deficits in surviving children.

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