5. Thomas S, Vijaykumar C, Naik R, Moses PD, Antonisamy B. Comparative effectiveness of tepid sponging and antipyretic drug versus only anitpyretic drug in the management of fever among children: A randomized controlled trial. Indian Pediatr 2009; 46: 133-136.

6. Falzon A, Grech V, Caruana B, Magro A, Attard-Montalto S. How reliable is axillary temperature measurement? Acta Paediatr 2003; 92: 309-313.

7. Fleisher GR. Textbook of Pediatric Emergency Medicine, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.

Iron Supplementation for Improving Mental Development

TARUN GERA AND *HPS SACHDEV

Consultant Pediatrics, SL Jain Hospital, Ashok Vihar Phase III, New Delhi 110 052;
**Senior Consultant Pediatrics and Clinical Epidemiology,Sitaram Bhartia Institute of Science and Research, B-16 Qutab Institutional Area, New Delhi 110 016, India. E-mail: hpssachdev@gmail.com*

In the absence of a simple, reliable and cheap indicator of iron status, anemia is invariably used to quantify the burden of this micronutrient deficiency in public health settings. Anemia is a major public health problem, particularly in the developing countries where nearly two billion individuals are affected, with a significant proportion being constituted by children and women of childbearing age(1). The etiology of anemia is multifactorial; however, from a public health perspective, iron deficiency is believed to be the most important causal factor. The World Health Organization estimates that roughly 50% of anemia prevalence can be attributed to iron deficiency(1). Evidence links iron deficiency to several functional consequences; an important one of these is mental and motor development in children.

Animal studies have provided a number of possible mechanisms through which iron deficiency can leave an imprint on the developing brain(2). Most observational studies in children have found associations between iron deficiency anemia and poor cognitive and motor development, and behavioral problems(3). Longitudinal studies consistently indicate that children who were anemic in infancy continue to have poorer cognition, school achievement, and more behaviour problems into middle childhood(4). However, the possible confounding effects of environmental factors, particularly poor socio economic background, prevent causal inferences from being made.

Sen, *et al.*(5) present evidence from a controlled intervention trial that iron and folic acid supplementation in children aged between 9 and 13 years leads to modest (1.5 to 2 units on a scale of 100) but significant improvement in the various cognitive tests. The benefits were greater in anemic subjects, those with higher hemoglobin increments and with better compliance, and with increasing frequency of supplementation. However, certain methodological and analytical issues need consideration while interpreting the findings. The authors did not rigorously evaluate important confounders of cognitive development (socio-economic status, parental educational background and slum conditions). They selected 'comparable' schools instead of evaluating these factors at an individual level. Unfortunately, the school setting was not exploited to minimize the 'compliance effect' by supervised administration of the intervention. This cluster randomized trial did not account for the design effect in analyses. The trial appears to be underpowered to detect a change of 1.5 to 2 units in the cognitive scores. Finally, after deciding on a specified sample size it is unclear why the cognitive testing was restricted to a random subsample comprising 60% of the participants. In view of these caveats, the conclusions cannot be qualified as robust.

Nevertheless, the findings of this trial are in consonance with the conclusions of a systematic review, which synthesized data from 17 randomized controlled trials(6). The review concluded that iron supplementation improves the 'mental development score' of children significantly but modestly (about 0.30 SD units, roughly equivalent to 1.5–2 units on a scale of 100) ; the benefits were greater in initially anemic or iron deficient subjects, with longer duration of supplementation (>1 month) and in older children (>2years). However, it would be prudent to recognize that the systematic review pertained to iron supplementation alone whereas the intervention in this trial comprised iron and folic acid. This raises the issue of relative contribution of iron and folic acid towards the documented improvement in hemoglobin and cognition.

In contrast to iron deficiency, there is scant information on the magnitude of folate deficiency and its contribution to the prevalence of anemia and poor neurocognitive development. Even the choice of intervention in national anemia control program, namely a combination of iron and folic acid in preference to iron supplementation alone, is based more on faith rather than sound scientific evidence. Conversely, a theoretical risk of neurological damage is recognized if folic acid is administered in the backdrop of undiagnosed vitamin B_{12} deficiency. There is negligible evidence about the cognitive benefits of folate administration from trials in children. However, recent meta-analyses have documented the effect of folic acid with or without B_{12} supplementation on cognition and dementia in adults(7,8). Pooled analyses from four randomized controlled trials showed no effect of folic acid administration on cognition or dementia, although there was lowering of homocysteine levels. Thus, the available evidence does not support a clear role of folate in improving cognition. It would therefore be reasonable to ascribe the improvement in cognition scores primarily to iron supplementation in the trial being commented upon(5).

In conclusion, notwithstanding the outlined caveats, this trial reaffirms the role of iron supplementation in improving cognition in older children, especially those who are anemic. The potential reversibility of cognitive deficit with supplementation lends support to advocacy for public health programs to control iron deficiency.

Funding: None.
Competing interests: None stated.

REFERENCES

1. WHO/UNICEF/UNU. Iron deficiency anaemia: assessment, prevention, and control. Geneva, World Health Organization, 2001 (WHO/NHD/01.3). Available from: http://www.who.int/nut/documents/ida_assessment_prevention_control.pdf. Accessed Dec 27, 2008.
2. Beard JL, Connor JR, Jones BC. Iron in the brain. Nutr Rev 1993; 51: 157-170.
3. Lansdown R, Wharton BA. Iron and mental and motor behaviour in children. In: Iron, Nutrition and Physiological Significance: Report of the British Nutrition Task Force. London: Chapman and Hall; 1995. p. 65-78.
4. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr 2001; 131: 649S-668S.
5. Sen A, Kanani SJ. Impact of iron folic acid supplementation on cognitive abilities of school girls in Vadodara. Indian Pediatr 2009; 46: 137-143.
6. Sachdev HPS, Gera T, Nestel P. Effect of iron supplementation on mental and motor development in children: systematic review of randomized controlled trials. Public Health Nutr 2005; 8: 117-132.
7. Malouf M, Grimley EJ, Areosa SA. Folic acid with or without vitamin B12 for cognition and dementia. Cochrane Database Syst Rev 2003; 4: CD004514.
8. Balk EM, Raman G, Tatsioni A, Chung M, Lau J, Rosenberg IH. Vitamin B6, B12, and folic acid supplementation and cognitive function: a systematic review of randomized trials. Arch Intern Med 2007; 167: 21-30.