Iron Deficiency, Febrile Seizures and Brain Development

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Iron deficiency anemia is one of the most prevalent micronutrient deficiencies in young children in India and other parts of the world, and it is strongly associated with persistent cognitive and motor delays even after the anemia and iron deficit have been repaired. Madan, *et al.* [1] reported recently that children aged 6-23 months with moderate to severe iron deficiency anemia had lower mental and psychomotor scores that persisted to as long as 19 years of age. These children also had lower scholastic achievement and needed more special education assistance than iron sufficient children. These impairments may be related to several effects of iron deficiency in the developing brain including altered development of neurons in the hippocampus that encodes memories, impaired energy metabolism, delayed maturation of myelin, and slowed visual and auditory evoked potentials [2]. Iron deficiency has also been associated with alterations in synaptic neurotransmitter systems including norepinephrine, dopamine, serotonin, glutamate and gamma-aminobutyric acid (GABA). In addition, a paper by Kumari, *et al*. [3] in this issue of *Indian Pediatrics* provides evidence that iron deficiency is also a risk factor for febrile seizures in children 6 months to three years of age. This carefully done case-control study with a large sample size showed a highly significant association between iron deficiency and febrile seizures. As expected, a family history of febrile seizures or epilepsy in first degree relatives was also linked to the occurrence of febrile seizures in these children. The findings are consistent with another recent case-control study from Kenya of children 3-156 months of age, which reported that iron deficiency is a risk factor for simple febrile seizures but not for other types of acute seizures [4]. An important practical lesson from this study is that preventing iron deficiency may be an effective way to reduce the incidence of febrile seizures.

These new data are also important because they suggest that there may be a mechanistic link between febrile seizures associated with iron deficiency and two other disorders that cause enhanced brain excitability: restless leg syndrome (RLS) and attention deficit hyperactivity disorder (ADHD). RLS occurs in children and adults and is characterized by an urge to move the legs, usually associated with an unpleasant sensation while lying down for sleep at night [5]. Family studies and genome wide association studies suggest a genetic contribution to RLS, but it is also strongly associated with reduced serum ferritin levels, and magnetic resonance imaging (MRI) has shown reduced iron stores in brain in many patients. Altered metabolism of dopamine also appears to play a role in enhanced neuronal excitability in spinal motor and sensory nerves in RLS, and it usually responds well to dopaminergic agonists along with replenishment of iron. Iron deficiency has also been implicated in the pathogenesis of ADHD. Juneja, *et al*. [6] reported that there was a significant negative correlation between serum ferritin levels and the Connors Rating Scale for ADHD. Low iron levels have also been measured in the thalamus of children with ADHD using MRI, and the serum ferritin level has been shown to predict the optimal dose of amphetamine needed to treat ADHD. Gilbert, *et al*. [7] recently reported that children with ADHD have impaired cortical inhibition in response to transcranial magnetic stimulation that correlates with the severity of ADHD. These three disorders, febrile seizures, RLS and ADHD, may reflect different facets of altered brain excitability that is enhanced by iron deficiency and also influenced by genetic factors. Iron is clearly important for brain development as well as for prevention of anemia, and more study is warranted to understand its role in these common neurodevelopmental disorders.

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Childhood Mood Disorders: Myth or Reality

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The concept of depressive syndrome and mania that is distinct from the broad class of childhood onset emotional disorders has a relatively short history. In the past it was felt that children, for theoretical reasons such as 'immature personality structures' could not experience extremes of mood. Depression in adolescents was viewed as a normal feature of development, so-called 'emotional turmoil'. However, the last two decades saw intensive research in this area which has lead to a reappraisal of the concept of childhood depression and its difference from adolescent depression. In contrast to adolescent depression, pre-adolescent depression is less likely to lead to adult depression, has more overlap with other disorders, is less prevalent, shows a male preponderance and is more strongly associated with family dysfunction [1].

The clinical presentation of bipolar-disorder (BD) in the pre-adolescent and early adolescent age groups is greatly debated, although mid- to late-adolescent–onset BD is considered similar to adult BD [2]. Apart from the classical descriptions of bipolar disorder, children presenting with ''affective storms,'' mood lability, severe irritability and temper outbursts, symptoms of depression, anxiety, hyperactivity, poor concentration, and impulsivity with or without clear episodicity, can attract the DSM IV diagnosis of bipolar disorder- not otherwise specified (BD-NOS) [3]. Over the past decade, there is a surge in the numbers of children and adolescents diagnosed with BD in USA. However, there is a considerable transatlantic debate and European skepticism over the high prevalence of pediatric BD in the US [2]. A large epidemiological study in the UK did not detect any cases of pre-adolescent mania. Studies in psychiatric hospitals found BD in 0.0006% of hospitalized patients in Finland, 1.2% in Denmark, and 2.5-4.2% in India [4].

Additionally, the treatment for pre-pubertal affective disorder is controversial due to the limited evidence of the efficacy and safety of mood-stabilizer and antipsychotic medications in this population [5]. Ethical challenges in conducting clinical trials of psychotropic medications in children [6] and Blackbox warnings against the use of certain anti-depressants in this group has guidelines focusing on the efficacy of psychotherapy in depression [1] and off label clinical use of psychotropics. The proponents of the debate claim that the early detection and treatment of affective disorder would prevent adult morbidity and site examples from adult psychiatry literature of retrospective studies claiming that a high percentage of affective disorders have roots in childhood and adolescence. The skeptics claim that affect-dysregulation can be a symptom of a broad range of clinical condition like ADHD, conduct disorder, developmental trauma and misdiagnosis and pharmacological treatment may be detrimental [5].

In the background of such global controversies, this study by Sagar, *et al*. [7] gives an interesting insight in the Indian clinical scenario. Although the study is retrospective, it shows bipolar disorder as being less common than depression, half with an onset in early childhood, presentation age being <13 years, lack of major psychosocial stressors in majority of the cases and male preponderance. The study doesn't make clear distinctions in the clinical presentation between pre-pubertal and post-