Original Article

Iron deficiency anaemia in childhood and thyroid function

Prasong Tienboon MD, PhD and Kewalee Unachak MD

Department of Paediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

Studies in animals and adults have indicated iron deficiency anaemia to be associated with altered thyroid hormone metabolism. The aim of the present study was to determine the effect of iron deficiency anaemia on the thyroid function of young children. Concentrations of thyroxine (T_4) and triiodothyronine (T_3), free thyroid hormones (fT_4 and fT_3), thyroxine binding globulin (TBG), and thyroid stimulating hormone (TSH) were measured in the basal state and in response to an intravenous bolus of thyrotropin releasing hormone (TRH) in nine children one to three years of age with iron deficiency anaemia (IDA) before and after treatment with oral iron. The results of the anaemic children were also compared to basal and stimulated concentrations of thyroid hormones, TBG, and TSH of eight iron sufficient, age-matched children. Seven of the IDA and 6 of the control children were male. The mean haemoglobin (Hb) and serum ferritin (SF) in the IDA children at baseline were 93 g/L (range 81-102) and 6 μg/L (range 1-12) which increased to 121 g/L (range 114-129) and 54 μg/L (range 19-175), respectively, after a mean of 2.3 months (SD 0.5) of iron therapy. In the control group, mean Hb and SF were 125 g/L (range 114-130) and 51 μg/L (range 24-144), respectively. The basal values of TBG and thyroid hormones of the IDA children before and after iron treatment were not different from the control children. Similarly, there was no statistical difference in the thyroid hormones in the IDA children before compared to after resolution of the anaemia. Compared to the control children, the TSH response over time to TRH, TSH area under the curve (TSHAUC), and the peak TSH value after stimulation were all lower in the IDA children both before and after resolution of anaemia, but the differences were not significant. Iron therapy and resolution of anaemia had no effect among the IDA children. The time to reach the peak TSH concentration was longer in the IDA children ($P = 0.08$) than the control children before iron therapy. While the time to peak TSH decreased upon resolution of the anaemia, the difference was not significant. There was no effect of Hb concentration, age, or anthropometry with TSH, TSHAUC, or time to peak TSH after TRH stimulation in the IDA children before treatment. Normal thyroid function was preserved in these children with iron deficiency anaemia, however three of nine children had minor abnormalities of hypothalamic-pituitary function. These results indicate that hypothyroidism is unlikely to be a major cause of impaired psychomotor development or growth in young children with iron deficiency anaemia.

Key Words: nutrition, anaemia, iron deficiency, children, thyroid

Introduction

Iron deficiency is the most common nutritional disorder worldwide and affects millions of infants and children.[1] Several metabolic and functional consequences of iron deficiency have been described.[2-4] Studies in both animals and humans have shown poor thermoregulation to be one of these deleterious consequences and have implicated impaired thyroid hormone metabolism as a likely cause.[5-7] In a study by Beard *et al*, iron deficient anaemic rats had lower basal thyroid stimulating hormone (TSH) values and blunted TSH response to intravenous thyrotropin releasing hormone (TRH) injection.[8] Investigations in prepubertal patients with thalassemia major and adults with chronic renal disease have shown abnormalities in the pituitary-thyroid axis which reversed after blood transfusion and erythropoietin therapy, respectively.[9,10] The investigators of these studies considered this to suggest that the hypoxia of anaemia may cause or potentiate the adverse effect on the thyroid, perhaps by impairing the peripheral monodeiodinating system for thyroxine (T_4) conversion to triiodothyronine (T_3).[8,9] Iron deficiency anaemia and hypothyroidism in the first years of life are both associated with deficits in mental and motor development and poor growth, yet a relationship between iron deficiency and hypothyroidism has not been explored.[11,12] Studies performed to date are highly suggestive of a causal relationship, but because of limitations in research design there is no conclusive evidence that iron deficiency anaemia results in abnormal thyroid function or hypothyroidism. We now report the results of a prospective study designed to investigate this question.

Correspondence address: Dr. Prasong Tienboon, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand
Tel: 66-0-5389-5269; Fax: 66-0-5321-4437;
Email: prasong@chiangmai.ac.th
Accepted 8 November 2002

Materials and methods

Subjects and schedule of testing

Seventeen children aged one to three years were studied, nine with iron deficiency anaemia (IDA), but who were otherwise healthy, and eight sex- and age-matched healthy control children. A haemoglobin (Hb) concentration of <105 g/L as measured by the cyanmethaemoglobin method and serum ferritin (SF) of <12 μg/L as quantified by solid phase enzyme immunoassay were required for inclusion in the IDA group. IDA was confirmed retrospectively in all anaemic children by an increase in Hb of ≥10 g/L after the first month of iron therapy.[13-15] Informed consent was provided by the parent of each subject. The study protocol was reviewed and approved by the Human Ethics Committee of Chiang Mai University.

All children were admitted to the metabolic Ward of the Research Institute for Health Sciences, Chiang Mai University the day before the testing. Testing began between 08:00 and 09:00 hour the following morning after an overnight fast. All blood specimens were obtained through an indwelling intravenous catheter. Basal serum levels of thyroxine binding globulin (TBG), thyroxine (T_4), triiodo-thyronine (T_3), free T_4 (fT_4), free T_3 (fT_3), and thyroid stimulating hormone (TSH) were determined from specimens obtained 20 minutes before the intravenous injection over 15-30 seconds at time zero of 7 μg/kg thyrotropin releasing hormone (TRH). Multiple specimens were subsequently obtained for TSH at 20, 30, 45, and 60 minutes after TRH injection, and for TSH, T_4, T_3, fT_4, and fT_3 at 120 minutes. The mean of measurements from duplicate specimens were recorded as the observed value for all assays.

After initial testing, the children with IDA received ferrous sulfate (6 mg/kg elemental iron divided twice a day) which was to be taken by mouth with fruit juice for three months. The children were followed monthly after the initial testing and compliance to the treatment was assessed by quantifying ferrous sulfate remaining in the bottle at the follow-up visits. The IDA children were re-admitted for the second thyroid stimulation test upon confirmation of resolution of IDA (Hb >110 g/L and SF >20 μg/L). Control children were studied only once.

Hormone assays

All blood specimens were allowed to clot at room temperature and centrifuged. Sera were kept frozen at -20^0 C until being batch-assayed. Commercial radioimmunoassay kits were used to measure TBG, T_4, T_3, fT_4, fT_3 (Incstar Corp., Stillwater, MN). Intra-assay coefficient of variation (CV) of each assay was less than 7%. TSH levels were measured by an immunoradiometric assay (CoTube TSH IRMA, Bio-Rad, Anaheim, CA). Inter-assay and intra-assay CV's were 6.9% and 3%, respectively.

Statistical analysis

Group comparisons of continuous data were made by Students' t-test or Mann-Whitney U test. Differences in measurements before and after iron therapy in children with IDA were compared by paired t-test or Wilcoxon ranked sums. The integrated area under the TSH response curve (Area Under Curve - AUC) and the total TSH area were calculated for each TRH test.[16] Multiple regression was used to examine the effect of dependent variables of haemoglobin, age, anthropometry (% median weight for age, weight for height, and height for age according to National Center for Health Statistics (NCHS) standards[17] on baseline TSH, TSH AUC, and time to peak TSH after TRH). Data are expressed as mean and standard deviation (SD) unless otherwise noted, and statistical significance is defined as $P<0.05$.

Results

Seven of the 9 IDA and six of the 8 control children were male (Table 1). The mean Hb and serum ferritin (SF) in the

Table 1. Mean (SD) haemoglobin concentrations and basal levels of thyroid tests in nine children with iron deficiency anaemia before and after treatment and in eight control children

	IDA Before (A)	IDA After (B)	Control (C)	*P* value		
				A vs C	B vs C	A vs B
Age (mo)	18.4 (6)	20.7 (6)	23.9 (7)	0.10	0.33	<0.0001
Sex (M:F)	7:2		6:2			
Hb (g/L)	93 (8)	121 (5)	125 (6)	<0.0001	0.14	<0.0001
SF (μg/L)	6 (4)	54 (50)	51 (39)	0.0003	0.92	0.03
TBG (mg/mL)	33.9 (7)	33.7 (7)	31.6 (7)	0.52	0.55	0.94
T_4 (mg/dL)	9.38 (1.8)	9.47 (1.8)	10.29 (1.7)	0.31	0.36	0.85
T_3 (ng/dL)	166 (37)	163 (40)	159 (23)	0.63	0.78	0.85
FT_4 (ng/dL)	1.41 (0.3)	1.46 (0.3)	1.63 (0.3)	0.13	0.25	0.76
FT_3 (pg/mL)	4.13 (0.8)	3.60 (0.7)	3.91 (0.6)	0.54	0.34	0.09
TSH (mIU/mL)	1.46 (0.9)	1.61 (0.8)	2.04 (0.8)	0.23	0.29	0.55

IDA, iron deficiency anaemia; Hb, haemoglobin; SF, serum ferritin; TBG, thyroxine binding globulin; TSH, thyroid stimulating hormone.

IDA children at baseline were 93 g/L (range 81-102) and 129) and 54 μg/L (range 19-175) respectively, after a mean of 2.3 months (SD 0.5) of iron therapy. In the control group, mean Hb and SF were 125 g/L (range 114-130) and 51 μg/L (range 24-144), respectively. The initial (basal) values of TBG, free and total T_4, free and total T_3, and TSH of the IDA children before and after iron treatment were not different from the control children. Similarly, there was no statistical difference in the thyroid hormones in the IDA children before, compared to after, resolution of the anaemia.

Compared to the control children, the TSH response over time to TRH, TSH area under the curve, and the peak TSH value after stimulation were all lower in the IDA children both before and after resolution of anaemia, but the differences were not significant (Table 2). Individual anaemic children had subtle differences from the rest of their group. Children 1 and 6 had comparatively blunted TSH response to TRH with lower AUC and peak TSH. These responses improved after iron therapy in contrast to almost all other children in whom iron treatment resulted in lower rather than higher peak TSH and AUC. The mean time to reach peak TSH concentration was longer in the IDA children (P = 0.08) than the control children before iron therapy. While the time to peak TSH decreased upon resolution of the anaemia, the difference was not significant. There was no effect of haemoglobin concentration, age, or anthropometry with TSH, TSH AUC, or time to peak TSH after TRH stimulation in the IDA children before treatment (data not shown).

Table 2. Thyroid stimulating hormone response to thyrotropin releasing hormone in anaemic children before and after iron therapy compared to the healthy control children

	Time after administration (min)								
Subjects	0	20	30	45	60	120	AUC	Peak value (mU/L)	Time to peak (min)
IDA Before									
1	3.2	17.9	17.2	12.9	12.7	7.0	1393	17.9	20
2	0.7	6.0	5.2	4.1	3.5	1.5	399	6.0	20
3	1.4	12.8	13.2	8.9	8.1	4.2	934	13.2	30
4	1.4	13.0	13.1	10.9	8.1	3.9	955	13.1	30
5	2.7	20.4	21.1	19.5	15.3	8.5	1719	21.1	30
6	0.1	3.5	4.0	3.7	2.3	1.0	275	4.0	30
7	1.3	14.8	12.2	10.7	7.1	2.6	892	14.8	20
8	1.4	13.0	11.6	13.5	9.7	5.8	1092	13.5	45
9	1.0	8.1	7.6	7.8	10.0	8.0	959	10.0	60
Mean	1.5	12.2	11.7	10.2	8.5	4.7	958	12.6	31.7
(SD)	(0.9)	(5.5)	(5.5)	(4.9)	(4.1)	(2.8)	(443)	(5.4)	(13.2)
IDA After									
1	2.3	15.6	17.3	15.2	12.5	6.0	1351	17.3	30
2	2.1	8.2	8.0	6.0	4.9	2.2	583	8.2	20
3	1.7	11.8	11.3	7.8	6.5	3.0	783	11.8	20
4	1.3	10.7	12.0	9.6	8.3	3.6	884	12.0	30
5	3.1	19.5	21.4	20.8	16.9	8.1	1778	21.4	30
6	1.0	7.0	5.9	4.6	3.0	1.3	407	7.0	20
7	0.5	9.8	6.2	4.6	2.5	2.0	451	9.8	20
8	1.7	8.0	7.5	7.4	5.7	2.5	631	8.0	20
9	1.0	11.6	11.5	8.6	6.2	7.8	923	11.6	20
Mean	1.6	11.3	11.2	9.4	7.4	4.0	866	11.9	23.3
(SD)	(0.8)	(3.4)	(5.2)	(5.4)	(4.6)	(2.6)	(447)	(4.7)	(5.0)
Control									
1	2.8	17.5	18.4	12.6	10.4	4.3	1225	18.4	30
2	3.1	15.1	14.6	11.3	10.2	3.7	1100	15.1	20
3	2.4	12.5	10.4	10.0	7.4	2.9	856	12.5	20
4	1.3	15.0	12.4	9.9	6.2	1.6	822	15.0	20
5	2.0	13.8	14.4	11.3	9.7	4.1	1063	14.4	30
6	0.7	12.6	11.2	9.7	9.4	7.5	1059	12.6	20
7	1.6	15.4	10.6	12.6	7.0	4.2	957	15.4	20
8	2.4	12.4	11.4	10.4	7.6	3.0	883	12.4	20
Mean	2.0	14.3	12.9	11.0	8.5	3.9	996	14.5	22.5
(SD)	(0.8)	(1.8)	(2.7)	(1.2)	(1.6)	(1.7)	(139)	(2.0)	(4.6)

IDA, iron deficiency anaemia group; AUC, area under the curve.

Discussion

Normal thyroid function, as defined by normal levels of total and free T_4, total and free T_3, TBG, and baseline/early morning TSH, was preserved in our children with iron deficiency anaemia. This observation differs from that of other studies in which a causal relationship has been shown between anaemia and thyroid function. Lower T_4 and T_3 con-centrations and a suboptimal rise in serum T_3 in response to cold stress have been reported in adults with IDA.[6,7,18,19] Correction of anaemia after iron treatment partially normalized thyroid abnormalities and restored normal thermoregulation. Although these findings were interpreted to suggest that disordered thermoregulation was mediated by abnormal thyroid function, it is possible that thyroid hormone abnormalities in cold stress experiments are related to the effects of stress on catecholamine excretion by cold exposure rather than inherent thyroid dysfunction due to anaemia.[19,20]

An association between anaemia and thyroid dysfunction has also been shown in certain disease states. In a study by Ramirez *et al,* hemodialysis patients with chronic renal failure and renal anaemia had low concentrations of free T_4 and free T_3 which increased following treatment with erythropoietin.[10] Prepubertal children with thalassemia major demonstrated a rise in serum T_3 after correction of anaemia with blood transfusion.[9,12] Unlike our children, the anaemia in these patients was not due to iron deficiency, but was associated with thalassemia in which there is iron excess, or with chronic renal failure in which iron stores are not depleted. The reason for abnormal thyroid function and subsequent improvement after treatment in these conditions may be due to some as yet defined aspect of the underlying hemolytic or renal disease or a possible trophic action of therapeutic transfusion or erythropoietin rather than due to anaemia itself.[21]

Our results also indicate that tissue hypoxia due to anaemia is probably not a significant cause of thyroid dysfunction as has been previously postulated.[9] While we cannot exclude the possibility that thyroid function might be impaired with more profound iron deficiency and anaemia, the severity of anaemia in our children with IDA was similar to that in other studies which presented the tissue hypoxia hypothesis. However, it is worth noting that in our anaemic children at baseline there was a trend of longer time to reach peak TSH concentration in response to TRH, with one child (subject 9) showing a clearly abnormal response. Nevertheless, the values in the IDA children at baseline were not statistically different from either the post-treatment or healthy control children values. The abnormal baseline value of the one anaemic child was an exception/outlier, so it is not likely that even with a larger sample size a true difference in thyroid response would be identified. Interestingly, a few individual anaemic children showed subtle differences from the rest of their group in TSH and AUC in response to TRH, although a clinically meaningful difference is not apparent. These variances were unaffected by age, sex, severity of anaemia, weight for height, or height for age. While the tests used in these children are sufficient to identify abnormalities in thyroid function of clinical significance, however it is possible that newer and more sensitive methods to test hypothalamic-pituitary-thyroid function would have identified subtle thyroid dysfunction. A recent report suggests that the pattern of TSH surge at night is the most sensitive test in detecting subtle growth abnormalities associated with central hypothyroidism.[22] Both iron and thyroid hormone are critical for normal brain development. Impaired thyroid function leads to deleterious, permanent psychomotor deficits. The magnitude of these effects are dependent on the degree and duration of hypothyroidism before the onset of therapy. Thyroid hormone affects dendritic arborization and myelinization in the developing brain. As a result, hypothyroidism beyond five years of age, when brain maturation is almost complete, is not associated with permanent neurologic impairment.[23] Yet even in early life a significant hypothyroidism is required to bring about cognitive deficits, and in our patients with normal free T_4 and free T_3, cognitive deficits are not anticipated. Thyroid dysfunction is therefore unlikely to be an important cause of the impaired psychomotor development associated with IDA in young children.

Rather, a direct effect of iron deficiency on the developing brain is more likely. The role of iron in brain function is varied and includes the integrity of enzymes involved in oxidation-reduction, electron transport, and synthesis and degradation of neurotransmitters.[24] Iron concentrations are highest in the cortex, in the early postnatal period suggesting a critical role of iron in the developing brain. The identification of transferrin or transferrin-like substance in the rat pituitary gland is of interest, in view of the minor abnormalities observed in hypothalamic-pituitary function of a few of our children with IDA.[25]

In summary, the children in our study with IDA had normal thyroid function both before and after resolution of the IDA with iron therapy and compared to healthy control children. Individual children showed minor abnormalities in some parameters of hypothalamic-pituitary function, how-ever hypothyroidism with clearly subnormal free T_4 that causes psychomotor abnormalities in young children was not seen in our children with IDA. Based on the results of this study, it is apparent that the impaired mental and motor development observed in young children with IDA is not likely to be mediated by subnormal thyroid function. Consequently, causes other than thyroid dysfunction should be considered to explain the growth retardation associated with anaemia.

Acknowledgement

The authors sincerely thank G. Fuchs for his help in manuscript preparation.

References

1. DeMaeyer E. The prevalence of anaemia in the world. World Health Stat Q 1985;38:302-16.
2. Dallman PR. Biochemical basis for the manifestations of iron deficiency. Ann Rev Nutr 1986; 6: 13-40.
3. Cook JD, Lynch SR. The liabilities of iron deficiency. Blood 1986; 68: 803-9.
4. Scrimshaw NS. Functional consequences of iron deficiency in human populations. J Nutr Sci Vitaminol (Tokyo) 1984; 30: 47-63.
5. Beard J, Tobin B, Smith SM. Norepinephrine turnover in iron deficiency at three environmental temperatures. Am J Physiol 1988; 255: R90-6.
6. Beard J, Green W, Miller L, Finch C. Effect of iron-deficiency anaemia on hormone levels and thermoregulation during cold exposure. Am J Physiol 1984; 247: R114-9.
7. Beard JL, Borel MJ, Derr J. Impaired thermoregulation and thyroid function in iron-deficiency anaemia. Am J Clin Nutr 1990; 52: 813-9.
8. Beard J, Tobin B, Green W. Evidence for thyroid hormone deficiency in iron-deficient anaemic rats. J Nutr 1989; 119: 772-8.
9. Celani MF, Corradini MC, Rota C, Massolo F. A rise in haemoglobin levels may enhance serum triiodothyronine (T_3) concentrations in prepubertal patients with beta-thalassaemia major. Exp Clin Endocrinol 1990; 96: 169-76.
10. Ramirez G, Bittle PA, Sanders H, Bercu BB. Hypothalamo-hypophyseal thyroid and gonadal function before and after erythropoietin therapy in dialysis patients. J Clin Endocrinol Metab 1992; 74: 517-24.
11. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. N Engl J Med 1991; 325: 687-94.
12. Chwang L, Soemantri AG, Pollitt E. Iron supplementation and physical growth of rural Indonesian children. Am J Clin Nutr 1988; 47: 496-501.
13. International Committee for Standardization in Haematology. Recommendations for reference method for haemoglobinometry in human blood and specifications for international haemoglobincyanide reference preparation. J Clin Pathol 1978; 31: 139-43.
14. Linpisarn S, Kricka LJ, Kenedy JH, Whitehead TP. Sensitive sandwich enzyme immunoassay for serum ferritin on microtitre plates. Ann Clin Biochem 1981; 18: 48-53.
15. Driggers DA, Reeves JD, Lo EYT, Dallman PR. Iron deficiency in one-year-old infants: comparison of results of a therapeutic trial in infants with anaemia or low-normal haemoglobin values. J Pediatr 1981; 98: 753-8.
16. Celani MF, Montanini V, Marrama P. Effects of luteinizing hormone-releasing hormone (LRH) upon bioactive and immunoreactive serum LH in patients with Turner's syndrome before and after oestrogen treatment. Acta Endocrinol 1985; 109: 304-8.
17. Hamil PV, Drizd TA, Johnson CL, et al. Physical growth: National Center for Health Statistic Percentages. Am J Clin Nutr 1979; 32: 607-29.
18. Dillman E, Gale C, Green W, Johnson DG, Mackler B, Finch C. Hypothermia in iron deficiency due to altered triiodothyronine metabolism. Am J Physiol 1980; 239: R377-R381.
19. Martinez-Torres C, Cubeddu L, Dillmann E, Brengelmann GL, Leets I, Layrisse M, Johnson DG, Finch C. Effect of exposure to low temperature on normal and iron-deficient subjects. Am J Physiol 1984; 246: R380-R383.
20. Dillman E, Johnson DG, Martin J, Mackler B, Finch CA. Catecholamine elevation in iron deficiency. Am J Physiol 1979; 237: R927-R930.
21. Magro S, Puzzonia P, Consarino C, Galati MC, Morgione S, Porcelli D, Grimaldi S, Tancr D, Arcuri V, DeSantis V, Alberti A. Hypothyroidism in patients with thalassemia syndromes. Acta Haematol 1990; 84: 72-76.
22. Rose SR. Isolated central hypothyroidism in short stature. Pediatr Res 1995; 38: 967-73.
23. Macfaul R, Dorner S, Brett EM, Grant DB. Neruological abnormalities in patients treated for hypothyroidism from early life. Arch Dis Child 1978;53: 611-9.
24. Beard JL, Connor JR, Jones BC. Iron in the brain. Nutr Rev 1993; 51: 157-70.
25. Tilemans D, Vande Vijver V, Verhoeven G, Denef C. Production of transferrin-like immunoreactivity by rat anterior pituitary and intermediate lobe. J Histochem Cytochem 1995; 43: 657-64.