Iron supplemented formula milk related to reduction in psychomotor decline in infants from inner city areas: randomised study

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Abstract

Objective To compare the effect of unmodified cows' milk and iron supplemented formula milk on psychomotor development in infants from inner city areas when used as the main milk source.
Design Double blind, randomised intervention trial.
Setting Birmingham health centre.
Subjects 100 infants, mean age 7.8 months (range 5.7 to 8.6 months), whose mothers had already elected to use unmodified cows' milk as their infant's milk source.
Intervention Changing to an iron supplemented formula milk from enrolment to 18 months of age, or continuing with unmodified cows' milk.
Main outcome measures Developmental assessments using Griffiths scales at enrolment and at 18 and 24 months.
Results 85 participants completed the trial. There were no significant differences in haemoglobin concentration between the two groups at enrolment, but by 18 months of age 33% of the unmodified cows' milk group, but only 2% of the iron supplemented group, were anaemic ($P < 0.001$). The experimental groups had Griffiths general quotient scores that were not significantly different at enrolment, but the scores in both groups declined during the study. By 24 months the decrease in the mean scores in the unmodified cows' milk group was 14.7 whereas the decrease in the mean scores in the iron supplemented group was 9.3 ($P < 0.02$, 95% confidence interval 0.4 to 10.4). Mean subquotient scores were considerably lower in the unmodified cows' milk group at 24 months; significantly so for personal and social scores ($P < 0.02$, −5.4 to 17.2).
Conclusion Replacing unmodified cows' milk with an iron supplemented formula milk up to 18 months of age in infants from inner city areas prevents iron deficiency anaemia and reduces the decline in psychomotor development seen in such infants from the second half of the first year.

Introduction

Iron deficiency anaemia—that is, a haemoglobin concentration < 110.0 g/l—still occurs in 10 to 30% of preschool children living in inner cities in the United Kingdom.[1 2] There is a well established association between iron deficiency anaemia and developmental delay, and randomised studies providing oral iron supplements suggest that this may be causal.[3–8] We have previously shown that iron deficiency anaemia in infants and toddlers receiving unmodified cows' milk as their main milk source is eliminated by changing to an iron supplemented formula milk between 6 and 18 months of age.[9] Our study aimed to address an additional and pragmatic question: does randomisation to receive an iron supplemented formula milk between 6 and 18 months of age lead to an additional developmental advantage compared with continuing receipt of unmodified cows' milk? Detailed haematological and nutritional data from the study have already been published.[9] We now present the developmental outcomes.

Subjects and methods

Recruitment
Our keyworker (AD) received the names of all infants aged 6-8 months (567 identified) living in an inner city area of Birmingham from health visitors dealing with that area. AD visited the families, and the parents of only those infants whose mothers had already changed their infant's diet to unmodified cows' milk (n = 116) were asked to consider including their infant in the study. All mothers were given both verbal and written explanations of the study.

The mean age of infants at recruitment (47 boys and 53 girls) was 7.8 months (range 5.7 to 8.6 months). The population was 75% Caucasian, 24% AfroCaribbean, and 2% Asian (Indians). We excluded all preterm infants. Figure 1 shows the withdrawals and losses of participants from the study.

The participants lived in a socially deprived area with poor housing, high unemployment, and poor public amenities—locally there was only one bank and no large supermarkets. The small local shops were expensive and had limited stocks of food, particularly fresh fruit and vegetables.

Power calculation—We performed a power calculation, which showed that if 47 participants were allocated to each dietary group this would provide a study power of 95% at a significance level of 5% for a

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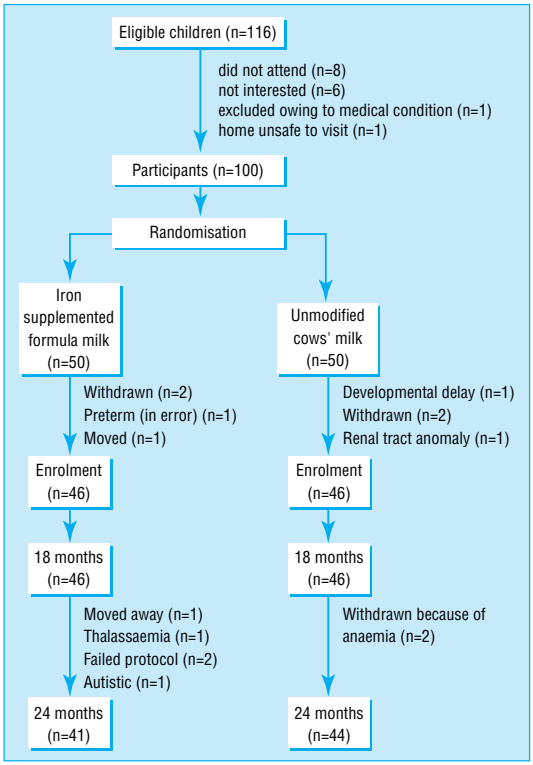

Fig 1 Withdrawals and losses from study

difference in haemoglobin concentration of 7.5 g/l between groups.

Study design

After recruitment we randomised the infants in the pharmacy department at Birmingham Children's Hospital by random numbers in blocks of four to receive either an iron supplemented formula milk or to continue on unmodified cows' milk. We gave the results of randomisation to AD who was therefore unblinded. At 18 months, those infants randomised to change to an iron supplemented formula milk were transferred back to cows' milk, and both groups continued on the cows' milk until 24 months of age. Serial haematological, anthropometric, and developmental assessments using the Griffiths scales were made at enrolment and at 18 and 24 months of age.[10] We excluded those participants whose haemoglobin concentration decreased to <90 g/l and referred them to their general practitioner.

We supplied the iron supplemented formula milk free of charge, and we gave those mothers whose infants remained on the cows' milk a monthly payment equivalent to the cost of 500 ml cows' milk daily. Mothers from both groups on income support were still entitled to claim free cows' milk with milk tokens. However, as not all parents were in receipt of income support, and therefore not entitled to the cows' milk, the cows' milk group received funding to purchase 500 ml cows' milk per day. Table 1 lists the nutrient content of the cows' milk and iron supplemented formula milk.

Developmental assessments

The Griffiths scale calculates an overall developmental score (general quotient), which is the mean of five subscales: locomotor, personal and social, hearing and speech, eye and hand coordination, and performance (manipulation and precision).[10]

Five trained and experienced observers performed the Griffiths scales. The observers were blinded to the group randomisations.

Statistical analyses—We performed statistical analyses with either paired and unpaired Student's *t* tests, χ^2 tests, or Fisher's exact tests, and analysis of variance.

Ethical approval—We obtained ethical approval from the South Birmingham Health Authority's ethics committee. We obtained informed written consent from caregivers.

Results

Withdrawals and losses

Some data points were missing due to intercurrent illness in a participant, transiently being unable to locate children, or insufficient volume of blood for assay. Out of 269 contacts, a developmental score was unavailable on 11 occasions (3%).

During the course of the study some children were found to have conditions that led their caregivers to withdraw them from the study. This was either because recommended treatment (for example, diet for an infant with renal disease) interfered with the study or because the diagnosis made continuing participation impractical (fig 1).

Sociodemographic characteristics of the study groups—After randomisation we found no significant difference between the two groups (table 2).

Haematology

At enrolment there were no statistically significant differences in mean haemoglobin concentration between the two groups; 16% of the cows' milk group and 13%

Table 1 Nutrient composition of unmodified cows' milk and iron supplemented formula (0.28 MJ of energy per 100 ml each)

Nutrient per 100 ml reconstituted feed	Unmodified cows' milk[11]	Iron supplemented formula
Protein (g)	3.2	2.1
Fat (g)	3.9	3.1
Carbohydrate (g)	4.8	8.0
Sodium (mg)	55	31
Potassium (mg)	140	89
Calcium (mg)	115	72
Magnesium (mg)	11.0	7.1
Phosphorus (mg)	92	58
Iron (mg)	0.05	1.2
Copper (μg)	Trace	43
Zinc (mg)	0.4	0.4
Chloride (mg)	100	58
Vitamin A (re) (μg)	52	80
Carotene (g)	21	24
Vitamin D (μg)	0.03	1.1
Thiamin B-1 (mg)	0.04	0.04
Riboflavin B-2 (mg)	0.17	0.15
Nicotinamide (mg)	0.1	0.65
Vitamin C (mg)	1	10
Vitamin E (tc) (mg)	0.09	0.48
Vitamin B-6 (mg)	0.06	0.04
Vitamin B-12 (μg)	0.4	0.2
Folic acid (μg)	6.0	7.0
Pantothenic acid (mg)	0.35	0.36
Biotin (μg)	1.9	3.0

re=retinol equivalent; tc=tocopherol.

Table 2 Characteristics of two study groups

Variable	Iron supplemented formula milk (n=50)	Unmodified cows' milk (n=50)
Maternal age at leaving education (years):		
16	38	41
17-18	9	6
>18	3	3
Mothers' age (years):		
<20	2	3
20-25	25	20
26-30	16	22
31-35	6	3
>36	1	2
Home ownership:		
Own home	2	1
Council owned house	18	20
Council flat	30	29
Income:		
Income support	31	28
Family credit	11	12
Parental smoking	34	31
No of siblings:		
1	19	16
2	8	11
3	3	5
4	2	1
>4	2	0

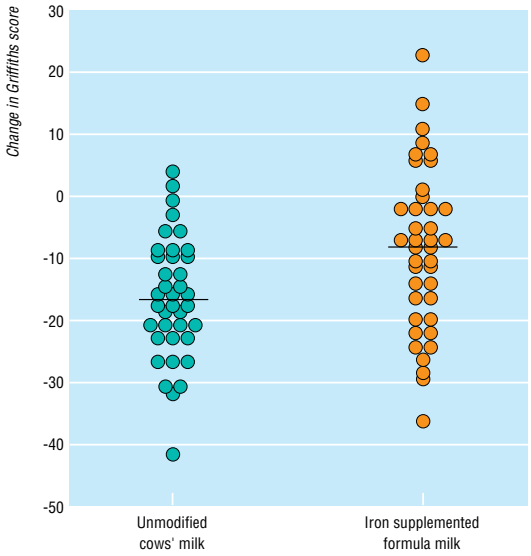

Fig 2 Changes in Griffiths general quotient score between enrolment and 24 months of age in infants receiving unmodified cows' milk or iron supplemented formula milk (P=0.02)

of the iron supplemented formula milk group were already anaemic.

By 18 months, 2% of the iron supplemented formula milk group and 33% of the cows' milk group were anaemic ($P<0.0001$). At 24 months, when the iron supplemented formula milk group had been returned to cows' milk for 6 months, 26% of the cows' milk group were anaemic but none of the iron supplemented formula milk group were anaemic ($P=0.0017$). Similar changes occurred in mean corpuscular volume and ferritin concentration: there was no difference at enrolment, but at 18 and 24 months there were significantly lower values in the cows' milk group.[9]

Developmental outcomes

Interobserver differences—We found no statistically significant differences when the developmental scores for the different observers were compared by analysis of variance for both iron supplemented formula milk and cows' milk groups.

Griffiths general quotient scores—At enrolment there were no significant differences between the two groups. Scores in each group declined during the study (table 3, fig 2). By 18 months the mean general quotient score had decreased by 8.3 ($P=0.002$) and 6.7 ($P=0.02$) points in the cows' milk and iron supplemented formula milk groups respectively.

By 24 months there had been a further decrease of 6.4 points in the mean score of the cows' milk group

Table 3 Analysis of developmental scores for unmodified cows' milk and iron supplemented formula milk groups from enrolment to 18 months (46 and 46 infants respectively) and from enrolment to 24 months (44 and 42 infants respectively)

		Enrolment-18 months		Enrolment-24 months	
	Enrolment mean	Mean difference	P value (95% CI) for difference between groups*	Mean difference	P value (95% CI) for difference between groups*
General quotient					
Unmodified cows' milk	109.2	–8.3	0.66 (–3.1 to 6.1)	–14. 7	0.036 (0.4 to 10.4)
Iron supplemented formula	111.5	–6.7		–9.3	
Locomotor					
Unmodified cows' milk	114.5	–7.2	0.47 (–4.7 to 10.1)	–20.0	0.98 (–4.1 to 12.2)
Iron supplemented formula	115.3	–4.4		–15.9	
Personal and social					
Unmodified cows' milk	113.4	–12.9	0.31 (–3.6 to 11.2)	–19.0	0.02 (1.2 to 16.8)
Iron supplemented formula	112.0	–9.1		–10.0	
Eye and hand coordination					
Unmodified cows' milk	110.8	–12.1	0.56 (–5.9 to 10.6)	–16.4	0.28 (–4.2 to 14.2)
Iron supplemented formula	108.8	–9.7		–11.3	
Hearing and speech					
Unmodified cows' milk	109.4	–6.7	0.49 (–4.6 to 7.5)	–13.5	0.1 (–1.5 to 12.8)
Iron supplemented formula	106.5	–5.3		–7.8	
Performance (manipulation and precision)					
Unmodified cows' milk	109.4	–4.8	0.21 (–7.1 to 8.8)	–7.1	0.09 (–1.3 to 15.0)
Iron supplemented formula	105.7	–3.9		–0.2	

*Change in scores between groups.

($P<0.001$), whereas a decrease of only 2.6 points had occurred in the iron supplemented formula milk group. The decrease in general quotient score between enrolment and 24 months was significantly greater in the cows' milk group than in the iron supplemented formula milk group (14.7 versus 9.3 respectively, $P<0.02$; 95% confidence interval 0.4 to 10.4) (fig 2).

Subquotient scores

At enrolment there were no significant differences in mean subquotient scores between the two study groups, but they declined in both groups throughout the study (table 3, fig 3).

The decrease in subquotient scores from enrolment was consistently greater in the cows' milk group than in the iron supplemented formula milk group, both at 18 and 24 months, and in all subscales. However, only the decrease in personal and social skills between enrolment and 24 months was significantly greater in the cows' milk group than the iron supplemented formula milk group ($P=0.02$).

Developmental scores and haematological status—There was no significant linear correlation between haemoglobin concentration and general quotient scores at 24 months. However, those participants allocated cows' milk were significantly clustered towards both a lower haemoglobin concentration and lower general quotient score than those receiving iron supplemented formula milk, who were clustered significantly towards both a higher haemoglobin concentration and general quotient score. Thus, of the 24 participants with both a haemoglobin concentration <120 g/l and general quotient score <100 at 24 months, 20 had received cows' milk. In contrast, 13 of the 16 with a haemoglobin concentration >120 g/l and a general quotient score >100 had received iron supplemented formula milk ($P<0.0001$).

Growth and nutrient intakes—Both groups grew satisfactorily on both the iron supplemented formula milk and the cows' milk.[9]

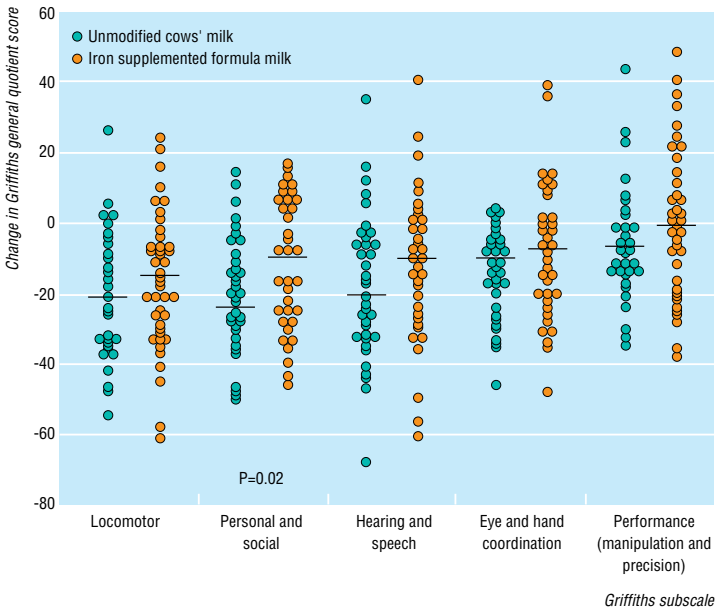

Fig 3 Changes in Griffiths subscales between enrolment and 24 months of age

Discussion

Our study shows that in a population of socioeconomically deprived infants, changing from unmodified cows' milk to an iron supplemented formula milk from 7 to 18 months of age prevented iron deficiency anaemia at 24 months, and significantly reduced the decline in psychomotor performance seen in those infants randomised to continue on cows' milk.

Nutritional basis of the observed effects—In contrast to other randomised studies, we chose to look at a realistic and practical dietary intervention.[6 7] We have previously shown that this intervention prevents the development of anaemia, but the precise nutritional basis of the developmental advantage in the group receiving iron supplemented formula milk is uncertain. The intakes of the two groups also differed substantially in nutrients other than iron.[9] However, the strength of the recognised association between iron deficiency anaemia and developmental delay, and the scale of the difference in iron status between the two groups, lead us to suggest that it is the disparity in iron status between the two groups that is the most plausible explanation for the observed difference in developmental performance.

Comparison with previous studies—Our findings support previous studies of supplementation with oral iron in children with iron deficiency anaemia, where an improvement in developmental performance was noted.[6 7 12] Moffatt and colleagues conducted a similar longitudinal cohort study to our own and showed a developmental advantage at 9 and 12 months, which was no longer detectable at 15 months of age.[8] The transient nature of the effect may have been due to differences in the timing, duration, and mildness of the iron deficiency compared with our study group.

Basis of the developmental advantage—The Griffiths scale has been well validated, and the subscales provide useful insights into the basis of the differences in developmental scores.[10 13] In our study the major difference was in the personal and social subscale. This supports the view that iron deficiency anaemia may exert its effects on developmental performance by alterations in affect, thereby making a child clingy, lethargic, irritable, and listless,[5] and leading to impaired learning skills.

Implications of the study—We acknowledge that it is difficult to quantify precisely the developmental advantage in the infants receiving iron supplemented formula milk, but nevertheless believe that this study has a number of important implications. Firstly, it confirms the well recognised observation that socioeconomic deprivation places infants at increased risk of adverse developmental outcomes.[14 15] Secondly, this developmental deficit seems, in part, to be nutritionally mediated. Thirdly, iron deficiency anaemia is common in high risk populations,[14] and both this and the developmental disadvantage are susceptible to a simple intervention: the provision of an iron supplemented formula milk in place of cows' milk.

Breast milk is clearly the milk of choice for the developing infant.[16] Our study suggests that in those mothers who find breast feeding impractical, iron supplemented formula milk seems to be effective and acceptable, and benefits high risk infants and children up to the age of at least 18 months.[15]

Key messages

- Iron deficiency anaemia is common in infants from inner cities who are given unmodified cows' milk in the first year of life
- Giving an infant iron supplemented formula milk instead of cows' milk not only prevents anaemia but reduces the decline in developmental performance observed in those given only cows' milk
- An iron supplemented formula milk rather than cows' milk should be provided free of charge for infants up to the age of 18 months who are living in inner cities and who are not receiving breast milk

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Contributors: IWB, AMacD, and AA had the original idea for the study, initiated it, and supervised its conduct. AD carried out the dietary intervention and data collection. TW took part in the developmental assessment and the preliminary data analyses. JW took part in the developmental assessment, collated and analysed the data and, with IWB, participated in writing the paper. IWB and JW will act as guarantors for the paper.

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1 Dalman PR. Nutritional anaemias in childhood. In: Suskind RM, Lweinter-Suskind L, eds. *Textbook of paediatric nutrition*, 2nd ed. New York: Raven, 1993.
2 Gregory JR, Collins DL, Davies PSW, Hughes JM, Clarke PC. National diet and nutrition survey: children aged 1½ to 4½ years. Volume 1. *Report of the diet and nutrition survey*. London: HMSO, 1995.
3 Lawson M. Iron in infancy and childhood. In: *Iron. Nutritional and physiological significance. Report of the British Nutrition Foundation task force*. London: Chapman and Hall, 1995.
4 Lansdown R, Wharton BA. Iron and mental and motor behaviour in children. In: *Iron. Nutrition and physiological significance. Report of the British Nutrition Foundation's task force*. London: Chapman and Hall, 1995.
5 Pollitt E. Iron deficiency and cognitive function. *Ann Rev Nutr* 1993;13:521-37.
6 Aukett MA, Parkes YA, Scott PH, Wharton BA. Treatment with iron increases weight gain and psychomotor development. *Arch Dis Child* 1986;61:849-57.
7 Idjradinata P, Pollitt E. Reversal of developmental delays in iron deficiency in infants treated with iron. *Lancet* 1993;341:1-4.
8 Moffatt MEK, Longstaffe S, Besant J, Dureski C. Prevention of iron deficiency and psychomotor decline in high-risk infants through use of iron-fortified infant formula: a randomised clinical trial. *J Pediatr* 1994;125:527-34.
9 Daly A, Macdonald A, Aukett A, Williams J, Wolff A, Davidson J, et al. Prevention of anaemia in inner city toddlers by an iron supplemented cows' milk. *Arch Dis Child* 1996;75:9-16.
10 Griffiths R. *The abilities of babies*. London: University of London Press, 1954.
11 Holland B, Welch AA, Unwin ID, Buss DH, Paul AA, Southgate DAT. *McCance and Widdowson's the composition of foods*, 5th ed. Cambridge: Royal Society of Chemistry, Ministry of Agriculture, Fisheries, and Food, 1991.
12 Lozoff B, Brittenham GM, Wolf AW, McClish DK, Kuhnert PM, Jimenez E, et al. Iron deficiency anaemia and iron therapy effects on infant developmental test performance. *Pediatrics* 1987;79:981-95.
13 Ramsay M, Fitzhardinge PM. A comparative study of two developmental scales: the Bayley and the Griffiths. *Early Hum Dev* 1977;1:151-7.
14 Aylward GP. The relationship between environmental risk and developmental outcome. *Dev Behav Pediatr* 1992;13:222-9.
15 Booth IW, Aukett MA, Iron deficiency anaemia in infancy and early childhood. *Arch Dis Child* 1997;76:549-54.
16 Hall D. *Health for children*, 3rd ed. Oxford: Oxford University Press, 1996.
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Commentary: Iron deficiency and developmental deficit—the jury is still out

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It has been estimated that around 10% of young children in the developed world and perhaps 50% in poor countries are iron deficient, with the burden falling disproportionately on less privileged children.[1] In their randomised controlled trial, Williams and colleagues report a 5.4 point smaller decline between 6-8 and 24 months in Griffiths developmental quotient in infants given iron supplemented feeds than in those given unmodified cows' milk (95% confidence interval 0.4 to 10.4). If, as this finding suggests, iron deficiency in infancy causes developmental deficit its prevention should be a public health priority.

This trial was small but generally well conducted: central randomisation ensured appropriate allocation concealment and assessment of outcome was blind to treatment group. It is unfortunate that a small number of children were excluded from analysis for what seem to be inappropriate reasons, including "failed protocol," "autism," thalassaemia, and anaemia. In small trials, exclusions after randomisation may be important in the interpretation of results, particularly where confidence intervals barely exclude 0. Interpretation is further complicated by the finding of virtually no difference between groups at 18 months.

The evidence from earlier studies is conflicting. A Canadian randomised controlled trial of iron supplementation in infants suggested a beneficial effect of supplementation at 9 and 12 months but not at 6 or 15 months and was weakened by substantial losses to follow up.[2] A randomised controlled trial of iron supplementation between 6 and 12 months in 944 previously breastfed infants found no differences between groups in Bayley scale scores at 12 months although iron deficiency anaemia was common in the unsupplemented group.[3] Two trials of iron treatment in toddlers with iron deficiency anaemia have reported on developmental findings 2-4 months after starting treatment. In a placebo controlled trial including 50 infants with iron deficiency anaemia, Idjradinata and Pollitt reported a significantly greater improvement in Bayley scale scores in the iron treated group.[4] However, Aukett and colleagues in a similar study found no significant differences between treated and control groups in changes in Denver developmental screening test scores although, as a result of inappropriate dichotomisation of continuous data, the study is frequently quoted as suggesting a positive effect of treatment.[5]

Although this trial tilts the balance of probability towards belief in a causal link between iron deficiency and developmental deficit, the evidence remains unclear. A call for more research may be interpreted as

an attempt to avoid decision making, but, particularly where interventions are costly or may have adverse consequences, clarity of evidence is essential. Prevention of iron deficiency is difficult. In spite of the high bioavailablity of iron in breast milk, both breastfed and bottle fed infants are at risk of developing iron deficiency unless sufficient iron is provided by the weaning diet. Dietary advice may not be effective in preventing iron deficiency anaemia,[6] and the administration of elemental iron may have side effects.[7] Large trials of both iron supplementation in infants and iron treatment in children with iron deficiency anaemia are urgently needed.

1 DeMayer E, Adiels-Tegman M. The prevalence of anaemia in the world. W*orld Health Stat Quart* 1985;38:302-16.
2 Moffatt MEK, Longstaffe S, Besant J, Dureski C. Prevention of iron deficiency and psychomotor decline in high-risk infants through the use of iron-fortified infant formula: a randomised clinical trial. *J Pediatr* 1994;125:527-34.
3 Lozoff B, De Andraca I, Walter T, Pino P. Does preventing iron deficiency anemia improve developmental test scores? *Pediatr Res* 1996;39:136A.
4 Idjradinata, P, Pollitt E. Reversal of developmental delays in iron-deficient anaemic infants treated with iron. *Lancet* 1993;341:14.
5 Aukett MA, Parks YA, Scott PH, Wharton BA. Treatment with iron increases weight gain and psychomotor development. *Arch Dis Child* 1986;61:849-57.
6 Childs F, Aukett A, Darbyshire P, Ilett S, Livera LM. Dietary education and iron deficiency anaemia in the inner city. *Arch Dis Child* 1997;76:144-7.
7 Idjradinata P, Watkins WE, Pollitt E. Adverse effects of iron supplementation on weight gain of iron-replete young children. *Lancet* 1994;343: 1252-4.

Genetic determination of islet cell autoimmunity in monozygotic twin, dizygotic twin, and non-twin siblings of patients with type 1 diabetes: prospective twin study

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Abstract

Objective To test the hypothesis that non-diabetic dizygotic and monozygotic twin siblings of patients with type 1 diabetes have a similar high prevalence of islet cell autoantibodies, thus suggesting that islet cell autoimmunity is mainly environmentally determined.
Design Prospective twin study.
Setting Two specialist centres for diabetes in the United States.
Participants Non-diabetic monozygotic twin (n = 53), dizygotic twin (n = 30), and non-twin (n = 149) siblings of patients with type 1 diabetes; 101 controls.
Main outcome measures Analysis of progression to diabetes and expression of anti-islet autoantibodies.
Results Monozygotic twin siblings had a higher risk of progression to diabetes (12/53) than dizygotic twin siblings (0/30; $P < 0.005$). At the last follow up 22 (41.5%) monozygotic twin siblings expressed autoantibodies compared with 6 (20%) dizygotic twin siblings ($P < 0.05$), 16 (10.7%) non-twin siblings ($P < 0.0001$), and 6 (5.9%) controls ($P < 0.0001$). Monozygotic twin siblings expressed multiple (≥ 2) antibodies more often than dizygotic twin siblings (10/38 *v* 1/23; $P < 0.05$). By life table analysis the probability of developing positive autoantibodies was higher among the monozygotic twin siblings bearing the diabetes associated HLA DQ8/DQ2 genotype than in those without this genotype (64.2% (95% confidence interval 32.5% to 96%) *v* 23.5% (7% to 40%) at 10 years of discordance; $P < 0.05$).
Conclusion Monozygotic and dizygotic twins differ in progression to diabetes and expression of islet cell autoantibodies. Dizygotic twin siblings are similar to non-twin siblings. These two observations suggest that genetic factors play an important part in determination of islet cell autoimmunity, thus rejecting the hypothesis. In addition, there is a high penetrance of islet cell autoimmunity in DQ8/DQ2 monozygotic twin siblings.

Introduction

Twin studies have contributed to our understanding of type 1 and type 2 diabetes mellitus.[1 2–7] Nevertheless, limitations of twin studies include small sample sizes and the potential for biased overascertainment of concordant twin pairs.[8 9] Such overascertainment is being dealt with by analysing twins identified through national registries[6 7] and by the prospective study of twin pairs discordant for diabetes at recruitment.[1–9]

Over the past decade a series of islet autoantigens have been cloned[10] and sensitive and specific autoantibody assays are now available.[11] Non-diabetic monozygotic twin siblings of patients with type 1 diabetes show a high prevalence of islet cell autoantibodies in most studies, ranging between 42% and 76%.[1 7 12] This finding is concordant with their high progression to diabetes. Most autoantibodies determined by radioassays are consistently expressed before diabetes develops, and most monozygotic twin siblings with multiple autoantibodies develop diabetes in the long term.[1 12]

Studies of dizygotic twins from all series, even with life table projections, indicate a low concordance rate for diabetes, between 0%[12] and 13%,[5 6] compared with 21% to 70% for monozygotic twins.[1 5 6 12] The highest rates for progression to diabetes in monozygotic twin siblings have been reported in studies with life table analysis and long term follow up.[1 7]

A recent report concerning Danish dizygotic twins indicates that as many as 77% of non-diabetic dizygotic twin siblings expressed GAD65, insulin, or cytoplasmic islet cell autoantibodies. The results of this study are surprising in that they suggest that the expression of islet cell autoantibodies is environmentally determined