British Heart Journal, 1973, 35, 87–92.

Folic acid deficiency in infants and children with heart disease[1]

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Twenty infants and children with cardiac disease including 15 with congenital heart disease and 5 with rheumatic disease were studied for signs of folic acid deficiency. Urinary formiminoglutamic acid (FIGLU) after a histidine load, and serum and whole blood folic acid activity were measured in each case. Six of the 20 had evidence of folic acid deficiency as determined by increased urinary FIGLU. Of the 6 with anaemia, 2 showed haematological response to folic acid therapy and the urinary FIGLU in these 2 returned to normal. Folic acid deficiency did not occur, as in adults, in only those with congestive heart failure. Malnutrition did not appear to be the sole cause of this deficiency since the diet and socioeconomic level of the folate deficient did not differ from that of the non-deficient cardiacs or controls. Diuretics and other medications received by these children could not be implicated as factors contributing to the vitamin deficiency. Regardless of the cause, this high incidence of folic acid deficiency in these children may have important consequences because of the role of this vitamin in growth and development.

Evidence of folic acid deficiency has been observed in adults with cardiovascular disease who did not appear to be malnourished. For example, Gräsbeck, Bjorksten, and Nyberg (1961) in a study of the urinary excretion of formiminoglutamic acid (FIGLU) in adults with folic acid deficiency noted that 5 patients with grave heart disease excreted abnormally high levels of FIGLU which were reduced to within normal limits after folic acid was administered. Similarly, Daly and Rose (1966) reported raised urinary FIGLU excretion in some adults in heart failure. Brody, Soltys, and Zinsser (1969) noted that 10 of 12 adults with congestive heart failure had low serum folate levels and evidence of megaloblastic changes in the bone marrow. Elman *et al.* (1970) measured serum folate levels in adults with nonmalignant diseases and found that in the group with myocardial infarction the mean level was lower than that for normal adults.

Many manifestations of cardiac disease in adults including myocardial infarct may also occur in infants and children (Franciosi and Blanc, 1968). In view of the importance of folic acid for growth and development, a group of infants and children with heart disease was studied for evidence of folic acid deficiency.

Received 10 July 1972.

[1] Supported in part by grants from National Institutes of Health.

Subjects and methods

The primary plan of this project was to determine the folic acid status of a paediatric cardiac population. The intent was to study this in 20 consecutive children with heart disease admitted to the paediatric services of the Flower and Fifth Avenue and Metropolitan Hospitals for either cardiac diagnosis or treatment. Because of the inadvertent early discharge of 2 children before studies were complete, 22 children were evaluated, but the 2 incomplete cases were not analysed. These subjects ranged in age from 6 weeks to 14 years.

There were 5 cases with rheumatic heart disease and 15 with congenital heart disease. The nature of these lesions is listed in Tables 1 and 2.

Besides the usual conventional *x*-rays and 13-lead electrocardiograms done on all patients, the 15 with congenital heart disease underwent cardiac catheterization and angiography. Of the rheumatic fever patients, the one with combined aortic and mitral insufficiency also had these last procedures.

All patients had analyses of blood glucose, blood urea nitrogen, and routine urines. When indicated, erythrocyte sedimentation rate, C-reactive protein, antistreptolysin O titre, serum complement, enzyme studies, stool analyses, and various cultures were done.

In order to compare the overall nutritional status of this group with the general population, heights and weights were plotted on the percentile chart developed by Dr. Harold C. Stuart.

Twenty-five infants and children of the same socioeconomic status who were in hospital for various medical

TABLE 1 *Folate deficient patients*

Case No.	Age	Diagnosis	Congestive heart failure	Percentiles		Urinary FIGLU (μg/ml / mg/24 hr)	Serum folate (ng/ml)	Whole blood folate (ng/ml)	Hb (g/100 ml)
				Wt.	Ht.				
6	11 mth	Congenital heart disease, persistent ductus arteriosus	0	25th	>25th	116·6 / 8	8	120·3	9·3 13·5
11	1 yr	Congenital heart disease; persistent ductus arteriosus + ventricular septal defect	Earlier +	25th	>10th	57·4	10·4	176·4	6·1
9	14 mth	Congenital heart disease; ventricular septal defect	Earlier +	<3rd	<3rd	31	6·2	82·5	9·4
18	7½ yr	Congenital heart disease; tetralogy of Fallot	Post-op. +	>3rd	25th	48 / 37	5·7	87·0	14·4
21	11 yr	Rheumatic heart disease; aortic insuffic. + mitral insuffic.	+	25th	>25th	33 / 37	17·4	154·2	13·6
10	14 yr	Rheumatic heart disease; mitral insuffic. + stenosis	0	>75th	>25th	40 / 56	6·7	63·2	12·2

TABLE 2 *Non-folate deficient patients*

Case No.	Age	Diagnosis	Congestive heart failure	Percentiles		Urinary FIGLU (μg/ml / mg/24 hr)	Serum folate (ng/ml)	Whole blood folate (ng/ml)	Hb (g/100 ml)
				Wt.	Ht.				
17	6 wk	Congenital heart disease; persistent ductus arteriosus + ventricular septal defect	+	10th	>10th	0·9 / 0·2	29·4	107·6	9·0
13	10 wk	Congenital heart disease; coarct., + endocard. fibro-elastosis	0	10th	25th	10·4 / 1·8	14·7	168·0	11·3
12	4 mth	Congenital heart disease; ventricular septal defect	0	3rd	<3rd	10·4 / 3·2	15·7	128·5	10·5
14	4 mth	Congenital heart disease; transposition gt. vessels	0	<3rd	>25th	10·4 / 4·7	18·7	240·3	18·0
4	7 mth	Congenital heart disease; ventricular septal defect	0	<3rd	3rd	8·7 / 1·4	12·6	118·5	9·4
20	2¼ yr	Congenital heart disease; ventricular septal defect	0	>25th	>25th	5·2 / 1·0	22·9	156·0	12·8
22	3¼ yr	Congenital heart disease; persistent ductus arteriosus	0	50th	>10th	6·2 / 1·6	12·6	127·1	13·0
2	3 7/12	Congenital heart disease; tetralogy of Fallot; pulm. atresia	+	>10th	50th	24·3 / 3·6	3·7	200·0	23·0
15	5½ yr	Congenital heart disease; mitral insufficiency	0	50th	>50th	7 / 2·2	28·1	85·1	11·8
16	6 yr	Congenital heart disease; aortic stenosis + mitral insuffic.	+	<3rd	>25th	17·4 / 1·7	16·7	158·4	12·8
1	9 yr	Rheumatic heart disease; mitral insuffic.	0	>75th	>97th	15·7 / 16·4	6·8	123·0	10·7
3	11 yr	Congenital heart disease; dextroversion + transpos. gt. vessels + single ventric. + pulm. sten.	0	<10th	90th	17·4 / 10·8	5·3	109·5	14·4
7	11 yr	Rheumatic heart disease; mitral insuffic.; myocarditis	+	>50th	>25th	8·7 / 14·6	8·5	85·5	10·0
8	13 yr	Rheumatic heart disease; mitral insuffic.; myocarditis	+	>50th	>50th	16·4 / 12·7	6·9	87·0	11·4

Heart size	*2° Diagnosis*	*Drugs*
Biventric. hypertrophy	Pneumonia	Penicillin; methicillin; fer-in-sol; folic acid
Rt. ventric. hypertrophy	—	Digoxin; fer-in-sol; folic acid
Biventric. hypertrophy	—	—
Rt. ventric. hypertrophy	—	Digoxin; chlorothiazide
Biventric. hypertrophy + left atrial enlargement	—	Digoxin; prednisone; penicillin
Upper limits of normal	—	Acetylsalicylic acid

Heart size	*2° Diagnosis*	*Drugs*
Biventric. hypertrophy	Upper resp. infect. + omphalitis	Digoxin; ampicillin
Lt. ventric. hypertrophy	—	Digoxin
Biventric. hypertrophy	Pneumonia	Penicillin
Rt. ventric. hypertrophy	Asymptomatic group B salmonella	Penicillin; digoxin; morphine
Biventric. hypertrophy	Pneumonia	Ampicillin; methicillin; ephedrine; sat. sol. KI
Biventric. hypertrophy	—	—
Normal	Asthma	—
Rt. ventric. hypertrophy	Resp. infect.	Digoxin
Lt. ventric. hypertrophy	Cong. ptosis rt. lid	—
Lt. ventric. hypertrophy	—	Digoxin; meralluride; morphine; quinidine
Upper limits of normal	—	—
Enlarged	Postcardiotomy syndrome	Oxacillin; codeine; digoxin; ampicillin; prednisone
Lt. ventric. hypertrophy + left atrial enlargement	—	Penicillin; prednisone; meralluride; chlorothiazide; morphine; digoxin; KCl
Lt. ventric. hypertrophy + lt. atrial enlargement	Organic brain syndrome	Chlorpromazine; penicillin; morphine; prednisone; meralluride

problems but without acute or chronic infection, diarrhoea, malignancies, or chronic haemolytic anaemia were also studied for signs of folic acid deficiency.

To assess folate status, a blood count, blood smear, serum and whole blood folic acid, and a urinary FIGLU determination were done on all cases. Reticulocyte counts, sickling test, haemoglobin electrophoresis, and erythrocyte glucose-6-phosphate dehydrogenase determinations were done in only a few cases. A bone marrow was done on only one patient.

Serum and whole blood folic acid activity were determined by microbiological assay using *Lactobacillus casei* as the test organism (Cooperman, 1967). Values below 4 ng per ml of serum and below 50 ng per ml whole blood are usually considered abnormal.

Urinary FIGLU excretion was determined after a histidine metabolic load (Luhby and Cooperman, 1964). Each child was given histidine hydrochloride monohydrate in amounts of 0·264 g per kg of body weight divided into 3 equal doses given 3 to 4 hours apart. For the infants, the histidine was dissolved in milk or milk formula. For the older children it was dissolved in apple juice. Urinary FIGLU values of 30 μg per ml or above, or 35 mg per 24 hour collection or above are indicative of folic acid deficiency. For infants where quantitative urine collections were not obtained only the concentrations of FIGLU (μg/ml) are given.

Results

Parameters of folic acid deficiency

Of the 20 patients, 6 had biochemical evidence of folic acid deficiency as evidenced by increased urinary FIGLU excretion (Table 1). The serum and whole blood folic acid activity of these 6 were within normal limits. Three (Cases 6, 9, and 11) had haemoglobin levels below 10 g/100 ml. Two of 14 in the non-folate deficient group also had haemoglobin levels below 10 g/100 ml. Peripheral blood smears were taken from each subject and examination of the smear of Case 11 indicated hypersegmentation of the neutrophils. A bone marrow aspiration was also obtained from this child and megaloblastic changes in both the red and white blood cells were seen in the stained preparations. The child had been given iron in therapeutic amounts for 3 months without a haematological response. She then received 5 mg folic acid per day orally, and after three days of therapy the FIGLU excretion returned to normal levels. This child also made a slight haematological response, the haemoglobin level rising in two weeks from an initial level of 6·1 g/100 ml to 7·7 g/100 ml, and the red blood cells from 2·3 to 3·4 million per mm^3. The patient however died in another hospital of cardiac arrest soon after and the complete haematological response could not therefore be followed.

Case 6 also failed to make a haematological response to a therapeutic regimen with iron. She was

then given 0·1 mg per day of folic acid intramuscularly. Her reticulocyte count reached a level of 5·8 per cent on the fourth day of therapy from an initial level of 1 per cent. She was sent home on the fifth day after initiation of therapy and the folic acid dosage was increased to 5 mg per day orally. Her haemoglobin level six days later was 11·1 g/100 ml compared to a level of 9·3 g/100 ml at the start of folic acid therapy and continued to increase reaching 13·5 g/100 ml after 2 months.

In the 25 children without cardiac disease the urinary FIGLU levels ranged from 0–27 mg/24 hr. Their serum and whole blood folic acid activities were all within normal limits.

Cardiac disease in study subjects

Among the 6 patients with evidence of folate deficiency, 4 had congenital heart disease; persistent ductus arteriosus, persistent ductus arteriosus combined with a ventricular septal defect, ventricular septal defect, and tetralogy of Fallot. The other two had rheumatic heart disease; 1 with aortic and mitral insufficiencies and the other with mitral insufficiency and stenosis. Four of these patients had congestive heart failure, 2 at the time of study and 2 earlier. Three of the 4 had congenital heart disease (Table 1).

Of the 14 who had no evidence of folate deficiency, 11 had congenital and 3 had rheumatic heart lesions (Table 2). Among the 11 with congenital heart disease, some had lesions similar to those in the group with folate deficiency. The 3 with rheumatic heart disease had isolated mitral insufficiency. Five of the 14 had congestive heart failure at the time this study was done; 3 with congenital heart disease and 2 with rheumatic heart disease.

Dietary and socioeconomic factors

The socioeconomic status of the folate deficient and the non-folate deficient patients was the same. The diet for all cases, as determined from dietary histories, did not appear to differ. Though the diets seemed to be nutritionally adequate, no attempt was made to determine food intake for each subject.

Among the folate deficient patients, 5 were below the 50th percentile for weight and all were below the 50th percentile for height. In the non-deficient group, 9 were below the 50th percentile for both weight and height.

Blood and urine chemistry

Fasting blood glucose, blood urea nitrogen, serum electrolytes, and CO_2 were within normal limits, with no differences between the folate deficient and non-deficient groups.

Discussion

Folic acid deficiency has been associated with a number of clinical entities (Luhby and Cooperman, 1964; Shaw and Hoffbrand, 1970). During the past decade several articles have appeared on the occurrence of folic acid deficiency in adults with heart disease usually associated with congestive heart failure.

In this study, we show for the first time that folic acid deficiency occurs with significant frequency in infants and children with various forms of congenital heart disease and rheumatic heart disease.

Occurrence and determination of folate deficiency

As shown in Table 1, 6 of the 20 patients had biochemical evidence of folate deficiency, as determined from the abnormally raised urinary FIGLU excretion after histidine load. Using the same parameter for folate deficiency, none of the infants and children in hospital without heart disease had evidence of folate deficiency.

In adults with cardiac disease associated with congestive heart failure, Gräsbeck *et al.* (1961) and Daly and Rose (1966) have also shown evidence of folate deficiency as determined by altered histidine metabolism. Gräsbeck *et al.* (1961) were also able to show a reduction of urinary FIGLU to normal levels after administration of folic acid to their patients.

Brody *et al.* (1969) reported that *L. casei* serum folic acid activity was low in 10 of 12 adults with cardiac disease. Elman *et al.* (1970) found that 13 adults with myocardial infarcts had low serum folic acid activity.

In this study, in contrast to those with adults previously cited, none of the children had low serum folic acid activity. The reasons for this difference are not at present clear. In a recent discussion of folate deficiency in adults with cardiac failure it was pointed out that serum folic acid activity may not reflect folic acid deficiency but rather is related to current dietary intake of the vitamin (*British Medical Journal*, 1970).

Similarly, the whole blood folic acid activity levels were within normal limits, even in those children who made haematological responses to folic acid therapy.

Since only 3 of the 6 children with biochemical evidence of folate deficiency had haemoglobin levels below 10 g/100 ml, it was not considered practical to study the haematological response to a therapeutic trial with folic acid in all cases. In one (Case 6) both a reticulocyte and haemoglobin response were observed after the child received physiological

amounts of folic acid. In another child with both biochemical evidence of folic acid deficiency and evidence of megaloblastosis in the bone marrow, a partial response was noted but this child was lost for further follow-up. Nevertheless, these observations and the reduction of urinary FIGLU to normal levels after folic acid therapy tend to confirm that folate deficiency existed in these children.

Growth and development

It can be noted that 5 of 6 folate deficient patients were below the 50th percentile in weight while all were below this percentile in length. Of the non-folate deficient group, 9 of 14 were below the 50th percentile in both weight and length. Statistical analysis showed that there were no significant differences between the two groups at both the 50th and 3rd percentile in weight and length.

The socioeconomic level was similar for the two groups and there were no discernible differences in the diets offered to these children, so that these factors alone could probably not account for the folic acid deficiency.

Cardiac disease

The heart lesions in both groups were strikingly similar. There did not appear to be a correlation between the age of the child, and therefore, in those with congenital heart disease, the duration of the disease and folate deficiency.

Two of the children with folate deficiency had congestive heart failure at the time of these studies. Two others manifested failure several months before but at the time of the study showed no evidence of this failure. Five of the 14 non-folate deficient subjects were in cardiac failure at the time of the folate studies. In these cases also, the lesions were similar (see Tables 1 and 2). When an attempt was made to correlate congestive heart failure with folate deficiency no statistical relation was found. This contrasts with the cited studies with adults, where practically all the folate deficients were in congestive heart failure.

Brody *et al.* (1969) have suggested that diuretics given to their patients in failure may have contributed to a more rapid elimination of folic acid and thus played a part in the folate deficiency. Only one of the folate deficient patients in our series received a diuretic while 3 of the non-folate deficients had also been given diuretics. Therefore, in our study, diuretics did not appear to be a factor. Digitalis could also not be implicated.

There have been several suggested causes for the folate deficiency in patients with heart disease. Hyde and Loehry (1968) found evidence for gastrointestinal malabsorption of folic acid in some of their patients with congestive cardiac failure. Elman *et al.* (1970), on the other hand, could find no defect in the gastrointestinal absorption of folic acid in a similar group of patients with low serum folic acid activity.

It has been suggested that the excessive urinary folate loss which may be the result of abnormal folate liberation from a liver damaged by chronic heart failure may contribute to the folate deficiency observed in these patients (Retief and Huskisson, 1969; Retief, 1970).

The mechanism whereby folic acid deficiency occurs in cardiac disease in adults has not as yet been elucidated. However, it is apparent that malnutrition alone does not account for this deficiency. It is clear that folate metabolism is altered in many patients with heart disease.

In children, folate deficiency occurs in a variety of cardiac conditions. Here, too, the cause of this deficiency does not appear to be solely malnutrition. However, in infants and children folate deficiency may be of important consequence because, in addition to being necessary for haematopoiesis, folic acid is essential for normal growth and development.

Folate coenzymes are necessary for purine, pyrimidine, and amino acid synthesis (Luhby and Cooperman, 1964). Adenosine triphosphate, a purine, important in cardiac function may well be linked with folate metabolism.

We wish to thank Drs. Robert Kahn and Arnold Slovis for permission to include several of their patients in this series. Our thanks also to Dr. A. Leonard Luhby in whose laboratory some of the studies were done and to Mr. Herbert Rich for his aid with the statistical analysis.

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