Urinary Excretion of Formiminoglutamic Acid in Children with Riboflavin Deficiency*

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Urinary excretion of formiminoglutamic acid following an oral dose of histidine was decreased in children with riboflavin deficiency than in those without it.

An increased excretion of urinary formiminoglutamic acid (FIGLU) following an oral dose of histidine has been reported in various conditions other than folic acid deficiency,¹ viz., vitamin B₁₂ deficiency,² hepatic cirrhosis,^{3,4} malabsorption syndrome,⁴ megaloblastic anemia associated with pregnancy and malnutrition,⁵ hemolytic anemia,⁶ iron-deficiency anemia,⁵ neoplastic disease,⁶ thyrotoxicosis,⁷ congestive cardiac failure,⁷ skin disorders,⁷ rheumatoid arthritis,⁸ toxemia of pregnancy,⁹ myelofibrosis,⁹ infants with protein malnutrition,¹⁰ a specific defect in gastrointestinal absorption of folic acid,¹¹ folic acid reductase deficiency,¹² formiminotransferase deficiency syndrome,¹³ and acute leukemia treated with amethopterin.¹⁴

In the present study urinary excretion of FIGLU following an oral histidine load was estimated on children who were deficient in folic acid and/or riboflavin, and the relationship among urinary FIGLU, serum folate and blood riboflavin levels was investigated. The results obtained revealed that there was a tendency to reduction of urinary FIGLU in children with riboflavin deficiency than in those without it.

METHOD AND MATERIALS

Sixty-two boys aged from 8 to 10 years were randomly selected from a primary school in Yokote village, Akita Prefecture, and subjected to estimation of serum *L. casei* folate activity,^{15,16} blood riboflavin¹⁷ and FIGLU¹⁸ in 3-hour urine following an oral dose of histidine-monohydrochloride, 0.33 g/kg of bodyweight.

It was found in our Laboratory that the mean value of blood riboflavin for normal children was $9.8 \pm 0.9 \gamma/100 \text{ ml}$.²⁰ In the present study, therefore, $9.0 \gamma/100 \text{ ml}$ was taken as a lower limit of normal blood riboflavin value. As regards serum *L. casei* folate levels $6.0 \text{ m}\gamma/\text{ml}$ ¹⁹ was taken as a lower limit in normal children.

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RESULTS AND DISCUSSION

According to the blood riboflavin and serum folate levels, the children examined were divided into four groups (Groups I–IV) (cf. Table 1).

Group I consisted of 22 boys with subnormal values of both serum folate and blood riboflavin.

Group II consisted of 10 boys who had the subnormal values of serum folate, but the normal levels of blood riboflavin.

Group III consisted of 13 boys who were normal for serum folate but subnormal for blood riboflavin.

TABLE 1. *Classification (Groups I–IV) according to serum folate and blood riboflavin levels*

Group	Number of cases	Serum folate (mγ/ml)	Blood riboflavin (γ/100 ml)
I	22	≤6.0	<9.0
II	10	≤6.0	≥9.0
III	13	>6.0	<9.0
IV	17	>6.0	≥9.0

Fig. 1

Fig. 2

Fig. 1. Urinary excretion of FIGLU following an oral dose of histidine in boys with various levels of serum folate and blood riboflavin.

Group I: Serum folate ≤6.0 mγ/ml, blood B₂ <9.0 γ/100 ml

Group II: Serum folate ≤6.0 mγ/ml, blood B₂ ≥9.0 γ/100 ml

Group III: Serum folate >6.0 mγ/ml, blood B₂ <9.0 γ/100 ml

Group IV: Serum folate >6.0 mγ/ml, blood B₂ ≥9.0 γ/100 ml

Black dots indicate the average for each group.

Fig. 2. Correlation between urinary FIGLU and serum folate levels in children with riboflavin deficiency (Groups I and III).

A significant correlation ratio of +0.35 was found.

TABLE 2. *Urinary FIGLU following an oral histidine load in boys aged 8 to 10 years and its relation to blood riboflavin and serum folate levels*

Group	No. of boys	Age (y.m.)	Serum folate (mγ/ml)	Blood riboflavin (γ/100 ml)	Urinary FIGLU (μ moles/3 hr)
I	1	8.4	5.3	5.8	5.1
	2	8.4	3.2	6.6	4.3
	6	8.4	4.7	7.0	29.3
	9	9.10	5.5	6.0	23.6
	10	9.4	4.6	5.2	10.4
	12	9.10	4.4	5.7	3.0
	14	9.4	2.7	6.0	11.5
	17	8.11	4.4	6.3	10.6
	24	9.11	4.8	6.9	25.8
	31	8.10	5.3	6.4	2.7
	32	8.9	3.1	5.8	3.8
	33	8.7	3.4	6.1	13.7
	5	8.4	6.0	7.9	12.2
	19	8.3	6.0	8.0	14.4
	20	9.0	5.2	7.3	17.3
	27	9.2	4.7	8.0	11.7
	34	8.8	3.9	7.5	8.6
	35	8.10	5.1	8.0	8.5
	39	9.3	5.5	8.0	16.8
	43	9.4	4.8	7.9	12.6
II	49	8.11	5.9	8.2	18.7
	16	9.10	4.0	7.2	7.8
	Average				12.4 ±7.5
	21	9.11	3.3	10.1	11.2
	22	8.4	4.7	9.3	44.0
	30	9.10	4.7	9.2	26.9
	41	9.11	6.0	9.8	7.2
	45	8.5	5.2	9.4	57.2
	55	8.2	4.8	10.4	1.0
	65	9.4	5.1	14.3	16.2
III	7	8.5	3.2	9.2	7.8
	15	10.0	2.1	9.8	5.2
	18	8.4	3.3	9.9	10.4
	Average				18.7 ±7.5
	4	9.8	6.4	5.7	6.0
	26	10.1	7.9	6.5	7.9
	29	9.10	10.4	5.6	28.4
	38	8.6	6.8	5.4	11.3
	53	8.6	6.4	5.7	35.8
	3	9.11	6.4	7.7	16.2
III	13	10.0	6.1	7.2	32.2
	23	9.10	8.0	8.5	18.7
	28	9.7	7.8	8.7	12.6
	40	9.8	8.1	7.5	34.6
	42	9.11	6.6	8.4	3.7
	48	8.7	6.9	7.9	6.2
	60	9.5	8.3	7.5	5.4
	Average				16.8 ±7.0

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Group	No. of boys	Age (y.m.)	Serum folate (mγ/ml)	Blood riboflavin (γ/100ml)	Urinary FIGLU (μmoles/3 hr)
IV	11	9.2	7.1	9.3	11.1
	25	10.2	8.0	9.7	14.3
	36	8.8	11.5	12.2	43.3
	37	8.1	9.2	10.7	4.6
	44	9.10	9.3	9.2	6.5
	46	8.3	8.9	9.1	25.8
	47	8.3	10.4	14.1	60.0
	50	8.4	15.5	10.1	19.8
	52	8.1	8.0	10.1	17.9
	54	8.10	10.4	9.6	7.0
	56	9.9	6.8	10.9	69.7
	57	9.3	6.8	12.9	12.8
	58	9.4	6.8	9.5	6.2
	59	10.1	11.6	10.5	29.8
	62	10.0	8.4	9.9	3.8
	64	10.1	6.4	11.7	7.2
	66	9.9	6.9	9.7	9.8
Average					20.5 ± 9.2

Group IV consisted of 17 boys who were of the normal levels of both serum folate and blood riboflavin.

Results of estimation of serum folate, blood riboflavin levels and urinary FIGLU following an oral dose of histidine in Groups I—IV were shown in Table 2 and Fig. 1.

When urinary FIGLU of 40 μmoles/3 hr or more was regarded tentatively as 'a high value of urinary FIGLU'; cases with the high urinary FIGLU were found in 2 out of 20 cases of Group II, but in none of Group I (cf. Fig. 1).

A similar tendency was also found when urinary FIGLU was compared between Groups III and IV; that is, cases with high urinary FIGLU were found in 3 out of 17 cases of Group IV, but in none of Group III (cf. Fig. 1).

These findings suggested that there was a tendency to reduction of urinary FIGLU in children with riboflavin deficiency irrespective of whether their serum folate levels were normal or subnormal.

Fig. 2 was a correlation table between urinary FIGLU and serum *L. casei* folate levels in children with riboflavin deficiency who were included in Groups I and III, and revealed a significant positive correlation ($r=+0.35$) between both items.

In other words, cases with lower serum folate levels in riboflavin deficient children showed lower urinary FIGLU values than those with higher serum folate. This finding seemed to be against the general conception¹ as regards the relationship between urinary FIGLU and serum folate levels that cases with low serum folate levels show high urinary FIGLU following an oral dose of histidine.

The data obtained, however, might be easily explained from the results of our animal experimentation,²¹ in which a marked reduction of urinary FIGLU

Fig. 3. Correlation between urinary FIGLU and serum folate levels in children free from ariboflavinosis. There was no significant correlation.

following an oral dose of histidine ensued in rats when fed on a riboflavin deficient diet for 11–30 days. A possible mechanism through which the reduction of urinary FIGLU occurred in riboflavin deficiency was an increased supply of tetrahydrofolate utilizable for the formiminotransferase reaction as a consequence of marked decrease in $N^{5,10}$ methylenetetrahydrofolate reductase activity induced by riboflavin deficiency.²¹

Fig. 3 showed no significant correlation ($r = +0.20$) between urinary FIGLU and serum *L. casei* folate levels in children free from ariboflavinosis who were included in Groups II and IV.

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