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## Abstract

To investigate the role of folic acid deficiency in the pathogenesis of anemia in the elderly, hematological examination and assays of serum iron, vitamin B12 and folate were carried out on the 86 elderly patients admitted to a home for the aged. Means of red blood cell counts, hemoglobin levels and hematocrit were  $385.3 \times 10^4/\text{mm}^3$ , 12g/dl and 36%, respectively. These levels were lower than any other report in Japan. Anemia was detected in 23 out of 86 patients. Judging from mean corpuscular volume and mean corpuscular hemoglobin, most of them were normocytic and normochromic. Although low serum levels of iron and folate were rather frequently observed, the results on hematological examinations suggest that deficiency of these factors alone is not the cause of the anemia in the elderly patients. Rapid clearance of 5-methyltetrahydrofolic acid and increased excretion of formiminoglutamic acid after histidine loading were revealed in some of those who had subnormal serum folate levels. Therefore, supplementation of folic acid is recommended to those who had poor dietary intake.

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## ANEMIA IN THE ELDERLY PATIENTS WITH SPECIAL REFERENCE TO FOLIC ACID STATUS

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*Abstract.* To investigate the role of folic acid deficiency in the pathogenesis of anemia in the elderly, hematological examinations and assays of serum iron, vitamin B<sub>12</sub> and folate were carried out on the 86 elderly patients admitted to a home for the aged. Means of red blood cell counts, hemoglobin levels and hematocrit were  $385.3 \times 10^4 / \text{mm}^3$ , 12 g/dl and 36%, respectively. These levels were lower than any other report in Japan. Anemia was detected in 23 out of 86 patients. Judging from mean corpuscular volume and mean corpuscular hemoglobin, most of them were normocytic and normochromic. Although low serum levels of iron and folate were rather frequently observed, the results on hematological examinations suggest that deficiency of these factors alone is not the cause of the anemia in the elderly patients. Rapid clearance of 5-methyl-tetrahydrofolic acid and increased excretion of formiminoglutamic acid after histidine loading were revealed in some of those who had subnormal serum folate levels. Therefore, supplementation of folic acid is recommended to those who had poor dietary intake.

Pathogenesis of anemia in the elderly are often complicated. There are three main factors (1) *i. e.*, (a) decrease of hematopoietic tissues and its function as a result of physiologic aging of the bone marrow (2), (b) shortening of the survival time of erythrocytes (3), and (c) deficiencies of hematopoietic factors such as iron, vitamin B<sub>12</sub> (B<sub>12</sub>) and folate including a lowering erythropoietin level. Although the assessment of iron (4), B<sub>12</sub> (5) and erythropoietin (6) were made on Japanese elders previously, no investigation has been done on folate status. High incidence of a folic acid deficiency in the elderly has been reported mainly from Britain (7-10). It is interesting to study whether or not folic acid deficiency among elderly population is common in Japan, because intake of this vitamin from diet is proved to be sufficient from the previous study by the authors (11). Purposes of the present paper are to report incidence of anemia in the elderly admitted to a geriatric hospital and to attempt to determine its cause(s) by assaying serum iron, B<sub>12</sub> and folate. Folic acid deficiency was confirmed further by the clearance test using active form of folate and by formiminoglutamic acid (FIGLU) excretion test after histidine loading.

## MATERIALS AND METHODS

Forty one male and 45 female patients over the age of 65 in a home for the aged were studied at the time of admission. Most of them were suffering from disablement caused by cerebrovascular accidents. No other disease which might influence the hematological data was detected by the examinations after admission. Conventional methods were employed for the hematological examinations including red blood cell count (RBC), hemoglobin level (Hb), hematocrit (Ht), white cell count (WBC), platelet count (PI) and reticulocyte (Ret) (12). Serum iron was estimated by the bathophenanthroline method (13). B<sub>12</sub> and folate were measured microbiologically using *Lactobacillus leichmannii* (14) and *Lactobacillus casei* (15) as test organisms, respectively. Normal ranges in our laboratory were 150-900 pg/ml and 3-15 ng/ml, respectively. Clearance of 5-methyl-tetrahydrofolic acid (5MTHF) (*d, l*-5-methyl-tetrahydropteroylglutamic acid which was provided kindly from Eisai Co. Ltd.) was performed on 12 elderly patients showing subnormal serum folate levels and on 5 healthy volunteers aging between 25 and 40 as controls. After the injection of 80 µg/kg of 5MTHF, serum folate levels were estimated at 5, 15, 30, 60 and 120 min. Excretion of folate into urine collected for 24 hr after folate loading was also studied. FIGLU excretion into urine during 8 hr after the administration of 15g of histidine was assayed according to Chanarin and Bennet (16) on 3 elderly patients with subnormal serum folate levels (1.9, 2.2 and 2.5 ng/ml each). Normal value for this test in our laboratory was below 17 mg/8hr.

## RESULTS

Mean levels of hematological values are shown in Table 1. Means of RBC, Hb and Ht indicated a decreasing tendency of these values in the patients studied. Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration were within normal range. Means of Ret, WBC and PI were also normal. Analysis of RBC, Hb, serum iron, B<sub>12</sub> and folate was listed in Table 2. Twenty three patients were found anemic by

TABLE 1. HEMATOLOGICAL EXAMINATIONS ON THE ELDERLY PATIENTS

Examinations	Mean	Standard deviation	Number of patients examined
Red cell counts ( $\times 10^4/\text{mm}^3$ )	385.3	61.0	86
Hemoglobin (g/dl)	12.0	1.7	86
Hematocrit (%)	36.0	4.9	71
MCV (fl)	93	9.8	69
MCH (pg)	31.2	3.7	86
MCHC (%)	33.6	3.1	70
Reticulocyte (%)	7.7	5.4	72
White cell counts ( $\times 1/\text{mm}^3$ )	6520	2795	84
Platelet counts ( $\times 10^4/\text{mm}^3$ )	16.9	11	65

TABLE 2. RED CELL COUNTS, HEMOGLOBIN LEVELS, SERUM IRON, VITAMIN B<sub>12</sub> AND FOLATE LEVELS IN ELDERLY PATIENTS

Examinations	Number of patients			Total number
	Low level	Subnormal level	Normal level	
Red cell counts ( $\times 10^4/\text{mm}^3$ )	0 ( $<200$ )	23 (200-350)	63 ( $>350$ )	86
Hemoglobin (g/dl)		26 ( $<11.2$ )	60 ( $\geq 11.2$ )	86
Serum iron ( $\mu\text{g}/\text{dl}$ )	16 ( $<50$ )	16 (50-70)	47 ( $>70$ )	79
Serum vitamin B <sub>12</sub> (pg/ml)	2 ( $<100$ )	7 (100-150)	69 ( $>150$ )	78
Serum folate (ng/ml)	2 ( $<1.5$ )	28 (1.5-3.0)	54 ( $>3.0$ )	84

Criteria for low, subnormal and normal in each item are shown in parenthesis.

applying the criterion of Shirakura (1). Serum iron was low in 16 (20.3%) and subnormal in 16 (20.3%) out of 79 patients. Low and subnormal B<sub>12</sub> levels were observed in 2 (2.5%) and 7 (9%) out of 78 patients, respectively. Low serum folate level was seen in 2 (2.4%) and subnormal level in 28 (33.3%) out of 84.

In order to elucidate the causes of the anemia, analysis of MCV, MCH, serum iron, B<sub>12</sub> and folate was attempted (Table 3). MCV and MCH were low

TABLE 3. ANALYSIS OF MCV, MCH, SERUM IRON, VITAMIN B<sub>12</sub> AND FOLATE LEVELS IN 23 ANEMIC PATIENTS

Examination	Range	Number of patients	Percentage of occurrence
MCV (fl)	$<86$	1	4.3
	86-99	18	78.3
	$>99$	4	17.4
MCH (pg)	$<29$	1	4.3
	29-35	18	78.3
	$>35$	4	17.4
Serum iron ( $\mu\text{g}/\text{dl}$ )	$<50$	7	30.4
	50-70	6	26.0
	$>70$	10	43.6
Vitamin B <sub>12</sub> (pg/ml)	$<100$	1	4.3
	100-150	1	4.3
	$>150$	21	91.4
Folate (ng/ml)	$<1.5$	1	4.3
	1.5-3.0	7	30.4
	$>3.0$	15	65.5

in only 1 patient. Serum iron of this patient was actually low, whereas B<sub>12</sub> and folate were normal. Obviously, this patient had iron deficiency. Among 4 patients showing high MCV and MCH, low levels of B<sub>12</sub> and folate were detected in 1 patient each. The third patient had subnormal serum folate and the fourth normal B<sub>12</sub> and folate. Although bone marrow examination was not carried out, at least, one patient was due to B<sub>12</sub> deficiency and 2 due to folate deficiency.

Interpretation of the results on 18 patients who had normal MCV and MCH was more complicated. A trial to classify these 18 patients by the values of hematopoietic factors is shown in Table 4. Serum iron was low in 5 patients and

TABLE 4. GROUPING OF 18 ANEMIC PATIENTS HAVING NORMAL MCV BY THE LEVELS OF SERUM IRON, VITAMIN B<sub>12</sub> AND FOLATE

		Number of patients			Total
		Low iron	Subnormal iron	Normal iron	
B <sub>12</sub> :	Subnormal	0	1	0	1
	Normal	5	3	9	17
Folate:	Subnormal	3	1	2	6
	Normal	2	3	7	12
Total		5	4	9	18

Criteria of low, subnormal and normal levels of each item are shown in Table 2.

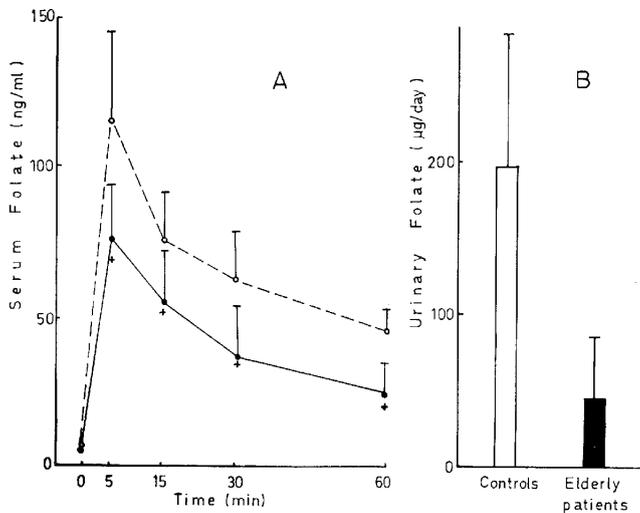


Fig. 1. Clearance test of 5-methyl-tetrahydrofolic acid (5MTHF) A: Serum folate levels after injection of 80 µg/kg of 5MTHF. ●—●; Means and standard deviations of 12 elderly patients. ○---○; Means and standard deviations of 5 controls. B: Urinary folate excretion during 24 hr after 5MTHF injection. +p<0.01.

subnormal in 4 patients. Serum folate was subnormal in 6 patients. Association of low serum iron and folate was seen in 3 patients.

Fig. 1 illustrates the clearance test of 5MTHF. Rapid clearance of 5MTHF from serum and decreased urinary excretion were observed in the elderly patients examined. As shown in Table 5, slightly increased excretion of FIGLU was revealed in 3 patients.

TABLE 5. FORMIMINOGLUTAMIC ACID (FIGLU) EXCRETION AFTER HISTIDINE LOADING

Case	FIGLU (mg/8 hr)
Elderly patients	
A	33.7
B	31.3
C	59.3
Patient with megaloblastic anemia due to folic acid deficiency*	110.5

\* Cited from Taguchi, H. *et al.*: *Blood and Vessel* **3**, 1115-1121, 1972 (in Japanese).

#### DISCUSSION

Mean levels of RBC, Hb and Ht reported in this paper are lower than any other report in Japan (3, 5, 17, 18, 19). High incidence of anemia in the studied population may be one of the reasons. Serum iron was low or subnormal in as many as 40.6% of the patients examined. Nevertheless, mean MCV and MCH were not so much low and only 1 patient out of 23 anemics showed low MCV and MCH. This fact indicated that iron deficiency was not a cause of anemia in the majority of the cases. Although confirmation of the above fact by assaying unsaturated iron-binding capacity is lacking, low serum iron may be due to an altered iron distribution by some factors such as latent chronic infection.

Low serum B<sub>12</sub> levels were rarely seen. Only 1 of 23 anemic patients was thought to be due to B<sub>12</sub> deficiency, though bone marrow examination was not done. As Katsunuma *et al.* reported (5), B<sub>12</sub> levels were not reduced in the majority of the cases. This finding in Japan is quite different from that in Denmark (20) where incidence of pernicious anemia is 1% in the aged population.

Incidence of subnormal serum folate was higher than expected. But, as seen in the analysis of the anemic patients, macrocytosis was not so frequent. Only 2 out of 23 patients are suspected to be due to folate deficiency assuming from MCV and serum folate levels, although this was not confirmed by bone marrow examinations.

In conclusion, the type of anemia were normocytic and normochromic in the

majority of the cases. Deficiencies of iron, B<sub>12</sub> and folate were not playing main role in the pathogenesis of the anemia in the elderly people.

Besides a high incidence of low serum iron mentioned above, low serum folate levels rather frequently seen in the present study needs comments. As recently reviewed by Chanarin (21), low serum folate only suggests a negative folate balance while many such patients still have adequate stores of folate. To our regret, red cell folate levels have not been assayed in the present study. But rapid clearance of 5MTHF and increased urinary excretion of F'GLU in some of the patients with subnormal serum folate suggest the fact that folic acid deficiency may well have been concerned with the pathogenesis of anemia. Confirmation of the above assumption by a response to folic acid administration is necessary.

Hurdle *et al.* (7) suggested that low serum folate is important as an indication of a degree of malnutrition in the elderly which might lead to megaloblastic anemia, if the body is challenged by diseases which increase folic acid metabolism. It is not surprising to observe such a high incidence of low serum folate in the elderly admitted to this hospital, if we assume the poor financial state, loneliness, apathy and inability to obtain enough foods because of infirmity as common in the elderly in Japan as in Britain (8, 22). Supplementation of folic acid should be tried for the elderly who have poor dietary intake.

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