

Acta Medica Okayama

Volume 32, Issue 4

1978

Article 1

AUGUST 1978

Megaloblastic anemia in Japan

Hirokuni Taguchi*

*Kochi Central Hospital,

Copyright ©1999 OKAYAMA UNIVERSITY MEDICAL SCHOOL. All rights reserved.

Megaloblastic anemia in Japan*

Hirokuni Taguchi

Abstract

Since 1903, 744 cases of megaloblastic anemia have been reported in Japan: 490 cases of pernicious anemia; 95 cases associated with pregnancy; 66 cases after gastrectomy; 22 cases of megaloblastic anemia of infants; 21 cases of folic acid deficiency other than pregnancy and 19 cases of vitamin B12 malabsorption after ileal resection. It is generally agreed among hematologists in Japan that pernicious anemia is relatively rare, as in other Asian countries. The diagnosis of pernicious anemia in Japan is usually made by stained marrow films, radioisotopic assay of serum vitamin B12, Schilling test and good response to vitamin B12 therapy. Serum folate level, intrinsic factor or its antibody, methylmalonic acid excretion, formiminoglutamic acid excretion and deoxyuridine suppression test are performed only at a small number of laboratories. The drugs of choice are hydroxocobalamin, deoxyadenosylcobalamin and methylcobalamin. Cyanocobalamin has nearly disappeared from commercial sources in Japan. Vitamin B12 administration is common in patients with neurological disorders. Megaloblastic anemia due to folic acid deficiency is extremely rare in Japan. Low serum folate levels are frequently observed among patients receiving anticonvulsants or in pregnant women, but in such samples megaloblastic anemia is almost never detected. The folic acid content of hospital diets indicates that satisfactory amounts of folate are taken in Japan. The intake of folic acid from rice is well over the minimum daily requirement of folate. Other factors in folic acid deficiency, such as food taboos, severe alcoholism and malabsorption syndrome are not frequently found in Japanese. The inadequate intake of folate was the critical factor in most reported cases.

KEYWORDS: megaloblastic anemia, vitamin B12, folic acid

Acta Med. Okayama 32, (4), 257—264 (1978)

MEGALOBLASTIC ANEMIA IN JAPAN

Hirokuni TAGUCHI

Kochi Central Hospital, Department of Medicine, Kochi 780, Japan

Received March 23, 1978

Abstract. Since 1903, 744 cases of megaloblastic anemia have been reported in Japan: 490 cases of pernicious anemia; 95 cases associated with pregnancy; 66 cases after gastrectomy; 22 cases of megaloblastic anemia of infants; 21 cases of folic acid deficiency other than pregnancy and 19 cases of vitamin B₁₂ malabsorption after ileal resection. It is generally agreed among hematologists in Japan that pernicious anemia is relatively rare, as in other Asian countries. The diagnosis of pernicious anemia in Japan is usually made by stained marrow films, radioisotopic assay of serum vitamin B₁₂, Schilling test and good response to vitamin B₁₂ therapy. Serum folate level, intrinsic factor or its antibody, methylmalonic acid excretion, formiminoglutamic acid excretion and deoxyuridine suppression test are performed only at a small number of laboratories. The drugs of choice are hydroxocobalamin, deoxyadenosylcobalamin and methylcobalamin. Cyanocobalamin has nearly disappeared from commercial sources in Japan. Vitamin B₁₂ administration is common in patients with neurological disorders. Megaloblastic anemia due to folic acid deficiency is extremely rare in Japan. Low serum folate levels are frequently observed among patients receiving anticonvulsants or in pregnant women, but in such samples megaloblastic anemia is almost never detected. The folic acid content of hospital diets indicates that satisfactory amounts of folate are taken in Japan. The intake of folic acid from rice is well over the minimum daily requirement of folate. Other factors in folic acid deficiency, such as food taboos, severe alcoholism and malabsorption syndrome are not frequently found in Japanese. The inadequate intake of folate was the critical factor in most reported cases.

Key words: megaloblastic anemia, vitamin B₁₂, folic acid

A relatively high incidence of pernicious anemia is found in northern Europeans and a low incidence in Russians, Italians, Greeks and Negroes have been reported (1). Japan has the lowest reported incidence of this type of anemia in the world. Three papers (2-4) on megaloblastic anemia statistics have appeared in Japan. One has been translated into German (5). Otsuka *et al.* (5) reviewed 309 cases reported between 1903 and 1953. Unfortunately the term "pernicious anemia" was used for all types of megaloblastic anemias; thus, the precise number of pernicious anemia cases in Japan is not known in foreign countries. Therefore, widely-distributed textbooks of hematology (6, 7) have not mentioned the incidence of megaloblastic anemia in Japan. The purposes of the present paper

are to review the number of reported cases of megaloblastic anemias in Japan during the period from 1903 to 1976, to comment on the reasons for its low frequency and on folic acid deficiency.

Reports on megaloblastic anemia in Japan. The precise incidence of megaloblastic anemia in Japan is not known. The three papers mentioned above report cases from 1903 to 1953 (2), 1960 (3) and 1963 (4). According to Kawakita (4), 353 cases have been reported in Japan in 69 years, including 215 cases of Addisonian pernicious anemia, 90 megaloblastic anemia associated with pregnancy, 19 post-gastrectomic patients, 13 infants, 2 bothrioccephalus infestations, 1 after ileum operation and 13 unclassified cases. Table 1 shows the total number to 1962 and the annual number of reported cases of each type of megaloblastic anemia from 1963 to 1976. The total number of 744 was obtained by adding the 391 cases since 1963. As in Europe and the United States, nearly two-thirds of the cases were pernicious anemia. The second largest group was megaloblastic anemia associated with pregnancy (12.7%). Surprisingly, 40 out of the 95 cases were reported by one group (Profs. Komiya and Kawakita at Kumamoto University) (8). Sixty-six cases (8.9%) were of megaloblastic anemia after gastrectomy. More than two-thirds of them appeared during last 14 years. Folic acid deficiency other than pregnancy is uncommon among Japanese. Only 21 cases have been recorded in 74 years; 5 of them were due to anticonvulsants. Twenty-two cases of megaloblastic anemia have been reported among infants and children, the well-known congenital enzyme deficiencies of folate reported by Arakawa's group are included (9). Cases of vitamin B₁₂ malabsorption by resection of the small intestine and blind loop syndrome have appeared during the past 14 years. Twenty-four cases were classified under unknown mechanisms, although folic acid deficiency was not completely excluded, because neither assay of serum folate nor therapy with a physiological dose of folate was performed in most cases.

Incidence of pernicious anemia in Japan. As shown in Table 1, 275 cases of pernicious anemia have been reported during the past 14 years (12.5 per annum). This number by no means represents the true incidence. No attempt has been made to analyse the incidence of pernicious anemia in Japan. Therefore, it is extremely difficult to assess the exact number of patients. It is generally agreed among hematologists in Japan that one case is encountered every one or two years in hospitals with 500-800 beds. In 5 years, 18 cases have been referred to the author from outlying hospitals in Okayama district, where nearly half million people reside. Even if the actual number of pernicious anemia patients in this area is three times our referrals (albeit groundless) the incidence of this anemia is calculated to be less than 10 per 100,000. At any rate, the incidence of pernicious anemia is very low in Japan compared to the United Kingdom and Scandinavia

Taguchi: Megaloblastic anemia in Japan

TABLE 1. REPORTED CASES OF MEGALOBLASTIC ANEMIA IN JAPAN

Year	Pernicious anemia	Post-gastrectomy	Intestinal operation	Blind loop syndrome	Pregnancy	Folate deficiency	Megaloblastic anemia of infants	Others	Total number
1903-1962	213	19	1	0	90	0	13	15	353
1963	19	2	1	0	0	0	1	0	23
1964	31	7	3	1	1	1	0	4	48
1965	14	1	0	0	0	0	0	0	15
1966	19	11	0	0	0	1	1	0	32
1967	25	1	1	1	0	4	0	0	32
1968	18	7	2	0	0	0	2	2	31
1969	22	1	1	0	0	0	1	1	26
1970	24	0	1	0	1	3	1	1	31
1971	25	3	0	0	0	1	1	0	30
1972	24	5	0	0	0	5	0	0	34
1973	9	6	4	3	0	3	0	2	27
1974	22	0	3	0	0	0	0	1	26
1975	7	3	2	0	2	1	1	0	16
1976	16	0	0	0	1	2	1	0	20
Total number	490	66	19	5	95	21	22	26	744
%	65.8	8.9	2.6	0.7	12.7	2.8	3.0	3.5	100.0

Megaloblastic Anemia in Japan

259

(100–180 per 100,000) (1). As pernicious anemia is a disease characterized by a lack of intrinsic factor from gastric juice, its occurrence is regulated by a genetic factor (1). Therefore, the reason for pernicious anemia being so rare in Japan may be due to similar genetic characteristics in Japanese and other Asians (1, 10–13). In addition, Japan is a relatively homogenous racial country; other ethnic groups living in Japan are Koreans (*ca.* 600,000) and Chinese (*ca.* 30,000). They also have low incidences of pernicious anemia. No differences were found in the sex and age distributions and in symptoms and physical characteristics in pernicious anemia patients in Japan compared to other countries.

Diagnosis and therapy of pernicious anemia in Japan. Most pernicious anemia cases in Japan are diagnosed by stained marrow films, a lack of acid in gastric juice and good responses to large amounts of vitamin B₁₂ administration. Schilling test is rather widely used. Assay of serum vitamin B₁₂ level using radioisotope has become popular recently. A microbiological assay of folate levels in serum and red cells is not commonly performed, except in a few laboratories. Intrinsic factor or its antibody assay is available at only a limited number of laboratories. Methylmalonic acid or formiminoglutamic acid (FIGLU) excretion test is used even less frequently. Deoxyuridine suppression test has only recently been introduced by the author (14). In Japan pernicious anemia therapy is usually carried out using 500–1,000 μ g of hydroxo-, deoxyadenosyl- or methylcobalamin. As these three types of compounds are easily available through commercial sources, cyanocobalamin has scarcely been used recently. Beck (7) claimed a vogue for oral and parenteral administrations of methylcobalamin to patients with neurological disorders in Japan. His view is correct, except that other types of cobalamins are also widely used to treat various neurological disorders. This practice is mainly based on a study of Kameyama *et al.* (15) reporting that oral administration of 1,500 μ g of methylcobalamin for 4 weeks was significantly effective in patients with peripheral neuritis compared to deoxyadenosylcobalamin and placebo. The validity of this clinical trial should be questioned because the only criterion of drug efficacy was a slight improvement in subjective symptoms and patients with a mild degree of vitamin B₁₂ deficiency were not excluded as the investigators did not assay serum vitamin B₁₂ levels.

Folic acid deficiency in Japan. Although 95 cases of megaloblastic anemia associated with pregnancy and 21 cases of other types of folic-acid deficiency anemia have previously been recorded, recently only 3 to 5 cases are reported per year. The majority of hematologists in Japan have the impression that folic acid deficiency anemia is extremely rare. So far, we have had experience with only 2 cases of megaloblastic anemia due to anticonvulsants (16) and 1 case due to pregnancy (17) respectively. In all three cases, an insufficient intake of folic acid was revealed in careful inquiry into past dietary history. This suggests that

the incidence of folic acid deficiency is influenced by nutritional factors. Investigations were then carried out on the folic acid status of patients receiving anti-convulsants (18) and in pregnant women (19). Surprisingly, no difference was observed in the frequency of subnormal serum folate levels between groups in Japan and in other countries having high incidences of megaloblastic anemia due to folic acid deficiency (20-22). Among 48 outpatients treated with anticonvulsants, 36 (75%) had subnormal serum folate levels. At the 36th week of pregnancy, 51 of 100 women showed subnormal serum folate levels. In spite of such a high frequency of subnormal serum folate level, no case of megaloblastic anemia was detected in the population studied. This discrepancy prompted us to carry out nutritional studies. The folic acid content of various foods in Japan was assayed (23). Using the results obtained, the dietary folic acid contents were calculated in three hospitals in the Okayama district (24). As listed in Table 2 with additional data from U. S. A. (25) and U. K. (26), the folic acid

TABLE 2. DIETARY FOLATE LEVELS IN THREE HOSPITALS IN JAPAN AND DATA FROM U. S. A. AND ENGLAND

	Free folate ($\mu\text{g}/\text{day}$)	Total folate ($\mu\text{g}/\text{day}$)
Japanese		
Hospital A	108	422
Hospital B	138	351
Hospital C	152	522
U. S. A. (Butterworth <i>et al.</i> (25))	157	688
England (Chanarin <i>et al.</i> (26))	160	676

contents of hospital diets in Japan were almost equal to family diets in U. S. A. and U. K. . Murata *et al.* (27) calculated the mean folic acid intake of 81 women living in Osaka as 176 $\mu\text{g}/\text{day}$ of free and 585 $\mu\text{g}/\text{day}$ of total folate. These results indicate that the folic acid intake of most Japanese was in a satisfactory range. The Japanese diet is usually composed of rice as a staple (nearly 30-40% of total calories), supplemented with fish, fresh vegetables, eggs, meats and fruits. We assayed the folic acid content of cooked rice (23) and obtained a free folate level of 5.5 $\mu\text{g}/100\text{g}$ and a total folate of 36.5 $\mu\text{g}/100\text{g}$. Thus in 1,000 g of rice, which is close to that consumed by ordinary Japanese each day, 55 μg of free and 365 μg of total folate are present. With an absorption rate of 80% for free (28) and 27% for total folate (29), 142.6 $\mu\text{g}/\text{day}$ of folate is available from 1,000 g of rice. This amount is well over the minimum daily requirement (30). The daily folic acid intake in a majority of Japanese is over this range. In addition, religious taboos on foods and patients with severe alcoholism and sprue are hardly found among Japanese. Therefore in Japan, megaloblastic anemia due to

folic acid deficiency is limited to exceptional cases under extremely poor dietary conditions for socio-economic or psychological reasons, even with other complicating causes of folate deficiency (*e.g.*, anticonvulsants, and pregnancy). Recent reports in Japan (31, 32) also suggest that an inadequate intake of folic acid plays the most important role in the manifestation of megaloblastic anemia.

Our observations in Japan and conclusion that megaloblastic anemia due to folic acid deficiency is extremely rare conflicts with the remark of Herbert (33) that "classic examples of dietary lack of folate are members of those ethnic groups around the world whose diet consists primarily or exclusively of rice." Can Japan be an exception? In 1972 we carried out a nutritional survey in Thailand (34). Interestingly, 89% of total calories were taken from rice by residents of the villages investigated. Among 607 villagers only 43 (7.1%) showed subnormal serum folate levels without any case of megaloblastic anemia. Sundharagiati (35) also reported a low incidence of folic acid deficiency among pregnant women in Bangkok. Herbert's assumption that folic acid content in rice is quite low may be derived from his experiment (36). He succeeded in producing experimental folate deficiency in man by giving a volunteer thrice-boiled rice as a staple food. He apparently lacks knowledge on the way rice is cooked in Japan, Thailand or other countries where rice is consumed as a staple food. In Japan and Thailand, rice is usually boiled with a small amount of water or steamed for a relatively short time; destruction of folate during cooking is not as great as he assumed. As a matter of fact, 13.8% of free and 36.5% of total folate is preserved by this way of cooking, whereas only 3.5% of free and 9.7% of total folate remain in rice boiled for 15 min with a large amount of water (37).

In conclusion, folic acid deficiency in Japan is associated almost exclusively with individuals with inadequate intake. Although anticonvulsants or pregnancy causes a decrease in serum folate levels, severe megaloblastic anemia does not occur if normal diet is followed. Generally speaking, in megaloblastic anemia of folate deficiency, an inadequate intake of folate is the most important factor. The geographic distribution of folic acid deficiency clearly depends on differences in dietary habits. The relatively high prevalence of folic acid deficiency in Britain cannot be explained without considering the tendency to overcook vegetables. In Asia, the incidence of folic acid deficiency should be discussed by ethnic groups and not by countries. Hibbard *et al.* (38) have reported that megaloblastic anemia associated with pregnancy is most frequently observed among Indians and most rarely among Chinese in a study of three ethnic groups (Indians, Chinese and Malays) in Singapore. They suggested that the differences were due entirely to dietary habits among the three groups. In any country or ethnic group, dietary factors should be carefully investigated in cases of megaloblastic anemia due to folic acid deficiency.

REFERENCES

1. Chanarin, I.: *The Megaloblastic Anaemias*. Blackwell, Oxford, 1969.
2. Otsuka, S., Koshiishi, Y., Naruto, K. and Kumai, K.: Statistics of pernicious anemia in Japan (1907-1953). *Saishin Igaku* **11**, 184-190, 1956 (in Japanese).
3. Wakisaka, G., Uchino, H., Ukyo, S., Akazawa, Y., Yamamoto, S., Ando, H., Sotobayashi, H. and Adachi, A.: Pernicious anemia and other megaloblastic anemias in Japan and therapy. *Naika* **6**, 212-221, 1960 (in Japanese).
4. Kawakita, Y.: Megaloblastic anemia and pernicious anemia in Japan. *Jpn. J. Clin. Hematol.* **5**, 132-143, 1964 (in Japanese).
5. Otsuka, S., Koshiishi, Y., Naruto, K. und Kumai, K.: Die Anaemia perniciosa in Japan (Statistik). *Acta Hematol.* **16**, 199-203, 1956.
6. Wintrobe, M. M.: *Clinical Hematology*, 7th ed., Lea & Febiger, Philadelphia, 1974.
7. Beck, W. S.: Vitamin B₁₂ deficiency. In *Hematology*, ed. Williams, W. J., Beutler, E., Erslev, A. J. and Rundles, R. W., McGraw Hill Inc., New York, pp. 307-334, 1977.
8. Kawakita, Y., Nozuhara, Y., Yamase, H., Takata, K., Sakamoto, Y. and Murakami, A.: Megaloblastic and macrocytic anemia associated with pregnancy. *Jpn. J. Clin. Hematol.* **1**, 760-772, 1960 (in Japanese).
9. Arakawa, T.: Congenital defects in folate utilization. *Am. J. Med.* **48**, 594-598, 1970.
10. Jayaratnan, F. J., Seah, C. S., Da Costa, J. L., Tan, K-K. and O'Brien, W.: Pernicious anemia among Asians in Singapore. *Br. Med. J.* **3**, 18-20, 1967.
11. Irvine, W. J., McFadzean, A. J., Todd, D., Tso, S. C. and Yeung, R. T. T.: Pernicious anemia in the Chinese: A clinical and immunological study. *Clin. Exp. Immunol.* **4**, 375-386, 1969.
12. Britt, R. P., Stranc, W. and Harper, C.: Pernicious anemia in Indian immigrants in the London area. *Br. J. Haematol.* **18**, 637-642, 1970.
13. Desai, H. G. and Antia, F. P.: Vitamin B₁₂ malabsorption due to intrinsic factor deficiency in Indian subjects. *Blood* **40**, 747-753, 1972.
14. Taguchi, H., Stafford, D. M. and Chanarin, I.: Deoxyuridine suppression test: A comparison of two methods and effect of thymidine on the incorporation of ³H-deoxyuridine into DNA in human bone marrow cells. *Acta Med. Okayama* **31**, 113-120, 1977.
15. Kameyama, M., Abe, K., Iida, M., Inokuchi, T., Oota, N., Otomo, E., Okada, T., Okamoto, S., Kito, S., Sakamoto, F., Shiozawa, R., Takahashi, K., Hirayama, K., Matsui, T., Miyazaki, M., Muro, T. and Watanabe, H.: Therapeutic effects of methylcobalamin on disorders of the spinal cord and peripheral nerves. *Rinsho to Kenkyu* **49**, 1963-1966, 1972 (in Japanese).
16. Taguchi, H.: Clinical and experimental studies on folic acid deficiency due to anticonvulsants. 1. Clinical and nutritional studies on megaloblastic anemia due to anticonvulsants. *Acta Med. Okayama* **25**, 537-550, 1971.
17. Hara, K., Taguchi, H., Kanbara, K., Yoshioka, H., Arimori, S., Sanada, H. and Iwasaki, I.: A case of megaloblastic anemia induced by pregnancy. *Jpn. J. Clin. Hematol.* **12**, 398-404, 1971 (in Japanese).
18. Taguchi, H.: Clinical and experimental studies on folic acid deficiency due to anticonvulsants. 2. Investigations on patients receiving anticonvulsants and experimental study on the effect of diphenylhydantoin on the absorption of folic acid in rats. *Acta Med. Okayama* **25**, 551-566, 1971.
19. Taguchi, H., Hara, K., Sanada, H., Iwasaki, I., Hiraki, K. and Wakimoto, S.: Folic acid status in pregnancy in Japanese women. *Acta Haematol. Jpn.* **34**, 128-136, 1971.
20. Reynolds, E. H.: Neurological aspects of folate and vitamin B₁₂ metabolism. In *Clinics in Haematology*, vol. 5, no. 3, ed. Hoffbrand, A. V., W. B. Saunders, London, pp. 661-725, 1976.

21. Kitay, D. Z.: Folic acid deficiency in pregnancy: On the recognition, pathogenesis, consequences and therapy of the deficiency state in human reproduction. *Am. J. Obstet. Gynecol.* **104**, 149-175, 1970.
22. Rothman, D.: Folic acid in pregnancy. *Am. J. Obstet. Gynecol.* **108**, 149-175, 1970.
23. Taguchi, H., Hara, K., Hasei, T. and Sanada, H.: Study on the folic acid contents of foods. (1) Folic acid contents of various foods. *Vitamins* **46**, 313-318, 1972 (in Japanese).
24. Sanada, H. and Taguchi, H.: Clinical aspects of folic acid deficiency with reference to anticonvulsant therapy, pregnancy and folate intake. *Acta Haematol. Jpn.* **36**, 527-531, 1973 (in Japanese).
25. Butterworth, C. E. Jr., Santini, R. Jr. and Frommeyer, W. B. Jr.: The pteroylglutamate components of American diets as determined by chromatographic fractionation. *J. Clin. Invest* **42**. 1929-1939, 1963.
26. Chanarin, I., Rothman, D., Perry, J. and Stratfull, D.: Normal dietary folate, iron and protein intake, with particular reference to pregnancy. *Br. Med. J.* **2**, 394-397, 1968.
27. Murata, K. and Miyamoto, T.: Folic acid contents of foods and its intake. *Vitamins* **48**, 205-206, 1974 (in Japanese).
28. Anderson, B., Belcher, E. H., Chanarin, I. and Mollin, D. L.: The urinary and faecal excretion of radioactivity after oral doses of ³H-folic acid. *Br. J. Haematol.* **6**, 439-455, 1960.
29. Perry, J. and Chanarin, I.: Absorption and utilization of polyglutamyl forms of folate in man. *Br. Med. J.* **4**, 546-549, 1968.
30. Herbert, V.: Minimum daily adult folate requirement. *Arch. Intern. Med.* **110**, 649-652, 1962.
31. Minakata, T., Muto, Y., Yamaguchi, H., Asai, I. and Tsukada, T.: Megaloblastic anemia due to folic acid deficiency after partial gastrectomy - Report of a case. *Jpn. J. Clin. Hematol.* **15**, 564-567, 1974 (in Japanese).
32. Tsuboyama, A., Sasaki, R., Takaku, F., Mizoguchi, H. and Miura, Y.: Megaloblastic anemia due to folic acid deficiency observed in a pregnant woman with hereditary spherocytosis. *Jpn. J. Clin. Hematol.* **17**, 1122-1127, 1976 (in Japanese).
33. Herbert, V.: The five possible causes of all nutrient deficiency: Illustrated by deficiencies of vitamin B₁₂ and folic acid. *Am. J. Clin. Nutr.* **26**, 77-88, 1973.
34. Taguchi, H., Hara, K., Hasei, T., Hatta, K., Mori, H., Sanada, H., Iwasaki, I. and Hiraki, K.: Investigations on nutritional anemia on thg farmers in north-eastern part of Thailand. Part 2. Medical survey. *J. Nagaya Women's Univ.* **20**, 265-303, 1974.
35. Sundharagiati, B., Lau, K. S., Devakul, K. and Swansri, S.: Serum folate and B₁₂ levels in pregnant Thai women of Bangkok. *J. Med. Assoc. Thailand* **51**, 748-751, 1968.
36. Herbert, V.: A paratable diet for producing experimental folate deficiency in man. *Am. J. Clin. Nutr.* **12**, 17-20, 1963.
37. Taguchi, H., Hara, K., Hasei, T. and Sanada, H.: Study on the folic acid contents of foods. (2) Loss of folate in foods by boiling. *Vitamins* **47**, 21-25, 1973 (in Japanese).
38. Hibbard, B. M. and Hibbard, E. D.: Anaemia and folate status in late pregnancy in a mixed Asiatic population. *J. Obstet. Gynecol. Br. Commonw.* **79**, 584-591, 1972.