

Megaloblastic anemia in North Africa

**We prospectively studied 478 patients with megaloblastic anemia living in Tunisia. Overall, 98% of patients had vitamin B12 deficiency. Pernicious anemia accounted for most of these cases, and median age at presentation was 45 years. Megaloblastic anemia occurred in 19 subjects under 15 years of age, and of these, nine had the Immerslund-Graesbeck syndrome.**

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The majority of cases of megaloblastic anemias result from deficiencies of either cobalamin (vitamin B12) or folate (vitamin B9). The relative etiological role of each vitamin deficiency is well established in western countries,<sup>1</sup> but only few data have been reported so far from developing countries. There may be significant variations between regions reflecting differences in dietary habits or in the occurrence of associated pathologic conditions and diversity in the genetic background of the affected populations.

For a long time, it has been considered that megaloblastic anemias in the tropics are more likely the consequence of folate deficiency due to malnutrition, multiple pregnancies, chronic hemolysis and alcoholism.<sup>2</sup> However, a large study conducted in Zimbabwe showed that cobalamin deficiency is the principal cause of megaloblastic anemia in Austral Africa.<sup>3</sup> Only small series have been reported so far from Arab countries.<sup>4</sup>

From January 1999 to December 2001, 478 consecutive patients (from two hematology departments) with megaloblastic changes in bone marrow smears were prospectively studied. Patients who had received cytotoxic drugs or presented overt myelodysplastic or malignant changes were excluded. Serum cobalamin levels (normal range: 118-716 pmol/L), serum folate levels (normal range: 3.4-38.4 nmol/L) and red blood cell (RBC) folate levels (normal range: 272-1952 nmol/L) were determined by radioimmunoassay methods (Simultrac® SNB-ICN pharmaceuticals, NY, USA).

A sample of 120 randomly selected patients, who had serum cobalamin deficiency, were investigated by the dual isotope Schilling test (Dicopac® test, Amersham Healthcare, Birmingham, UK). Ninety-four patients with proven pernicious anemia were screened for serum autoantibodies. The screening included autoantibodies to intrinsic factor tested by an enzyme-linked immunosorbent assay (Genesis Diagnostic, UK), autoantibodies to parietal gastric cells tested by indirect immunofluorescence on section of mouse stomach and autoantibodies to thyroid antigens tested by radioimmunoassay (Immunotec®, Czech Republic). Ninety-four sera from normal Tunisian individuals, matched for age and sex, were tested as a control group. These individuals had normal blood cell counts, normal serum cobalamin levels and normal folate levels.

Out of 439 patients in whom blood cobalamin and folate levels were determined, prior to any vitamin supplementation, 430 patients (98%) expressed low serum

**Table 1.** Demographic and biological findings in 430 cobalamin deficient patients and in 103 patients with pernicious anemia.

	Cobalamin deficiency	Pernicious anemia
Number of patients (Sex ratio M/F)	430* (1.04)	103** (1.19)
Age at presentation (years)		
Age range (Median)	1-90 (46)	8 - 79 (45)
25% and 75% percentiles	34 and 63	33 and 57.5
Serum cobalamin levels		
Range ( pmol/L)	2-116.9	4.2-104
(Mean±1 SD) ( pmol/L)	(41±23.9)	(41.6±21.6)
Serum cobalamin 0- 60 (pmol/L)	351 (86.3%)	87 (84.5%)
<i>Hematological findings</i>	<i>n (%)</i>	<i>n (%)</i>
MCV (fL) <100	49 (11.4)	11 (10.7)
100 ≤MCV (fL)<120	237 (55.1)	52 (51.5)
MCV (fL) ≥120	144 (33.5)	40 (38.8)
Hb (g/dl)<6	230 (53.5)	49 (47.6)
6 ≤Hb (g/dL) <12	186 (43.2)	48 (46.6)
Hb(g/dL) ≥12	14 (3.3)	6 (5.6)
Pancytopenia	170 (39.5)	38 (37.7)
anemia+leucopenia <sup>†</sup>	32 (7.4)	8 (7.7)
anemia+thrombocytopenia <sup>†</sup>	46 (10.7)	12 (11.7)
anemia	168 (39)	39 (37.8)
Serum autoantibodies <sup>‡</sup>		<i>n=(%)</i>
AAb to GPC		57 (60.6)
AAb to IF		40 (42.6)
AAb IF + AAb GPC		24(25.5)
AAb to thyroid		22 (23.4)
Chronic atrophic gastritis		79/81(97.5)
<i>Helicobacter pylori</i>		5/43 (11.6)

\*Out of 438 patients evaluated for vitamins B12 levels; \*\*out of 120 patients with low vitamin B12 levels evaluated by dual isotope Schilling test; <sup>†</sup>leukopenia is defined as a WBC less than 20×10<sup>9</sup>/L; <sup>‡</sup>thrombocytopenia is defined as platelets less than 150×10<sup>9</sup>/L; <sup>§</sup>Only autoantibodies to thyroid antigens were detected in 3% of normal individuals. MCV: mean corpuscular volume; Hb: hemoglobin; AAb: autoantibodies; GPC : gastric parietal cells; IF: intrinsic factor.

cobalamin levels. In 424 patients, this was a pure cobalamin deficiency. Pure folate deficiency was observed in only six patients (1.2%) (two children and four mentally invalid patients). The Schilling test established the diagnosis of pernicious anemia in 103 patients (86%) of serum cobalamin-deficient patients who had further testing. The demographic, biological and clinical findings in the 430 cobalamin-deficient patients and in the 103 patients with pernicious anemia are shown in Table 1.

In 13 cases reduced vitamin B12 absorption was not corrected by oral administration of exogenous intrinsic factor. Two patients had celiac disease, one patient had ulcerative colitis, two patients had intestinal lambliaisis and eight patients, aged 9 months to 7 years (median age 4 years), had Imerslund-Najman-Graesbeck disease.

Four psychiatric patients had normal cobalamin absorption. In these cases, the vitamin deficiency was likely due to malnutrition and low dietary intake.

Three patients had normal cobalamin and folate levels

and a normal Schilling test: (one child had Fanconi's anemia and two siblings had a genetic defect in cobalamin or folate metabolism). In our series, 100 patients with vitamin B12 deficiency out of 430 (23%) presented neurological and/or psychiatric manifestations. Their demographic, hematologic and biochemical presentations were not significantly different from those of the whole group of patients.

As expected, familial consanguinity was common in our series: 26.7% were born of parents who were first cousins, a rate that is similar to the average rate in Tunisia.

This study is one of the largest series reported so far on megaloblastic anemia in non-western countries. It revealed several interesting features of the disease in the southern Mediterranean-Arab region. Megaloblastic anemia appears to be a rather common hematologic disorder in North Africa. since almost 500 affected patients could be prospectively identified over a 3-year period in a country with 10 million inhabitants, corresponding to a crude incidence of 16.6 cases per million per year.

This disease was almost exclusively due to cobalamin deficiency. Folate deficiency appears very rare in our region, likely reflecting a high dietary intake of folate. In addition, alcoholism, a classic cause of folate deficiency, is rare for religious reasons. The Schilling test revealed that 86% of cobalamin-deficient patients could be classified as having pernicious anemia due to atrophic gastritis. The global picture of pernicious anemia in Tunisia is not significantly different from that reported from other regions of the world.<sup>5-8</sup> However, one should stress the relatively young age of the patients with this disease with almost 21.5% being less than 30 years old at the time of diagnosis.

As expected, a high rate of familial consanguinity and marriages between first degree cousins characterized our patients, reflecting the common endogamy in Arab societies. Consanguineous marriages favour the homozygous expression of recessive traits (e.g. the Immerslund-Graesbeck syndrome, which nine cases in our series had) and the occurrence of multigenic diseases (e.g. autoimmune diseases) and likely account for earlier expres-

sion of the pernicious anemia. Interestingly, two young patients aged 19 and 21 years old with cobalamin malabsorption corrected by oral intrinsic factor did not have atrophic gastritis. These patients may have a genetic defect in intrinsic factor excretion or excretion of a defective intrinsic factor as previously reported.<sup>9</sup>

Chokri Maktouf,<sup>1</sup> Fattouma Bchir,<sup>2</sup> Hechmi Louzir,<sup>3</sup>  
Moez Mdhaffer,<sup>5</sup> Moez Elloumi,<sup>5</sup> Hela Ben Abid,<sup>2</sup>  
Balkis Meddeb,<sup>3</sup> Faiza Makeni,<sup>5</sup> Adnene Laatiri,<sup>7</sup>  
Taoufik Soussi,<sup>5</sup> Aicha Hafsia,<sup>6</sup> Koussay Dellagi<sup>3,4</sup>

Departments of Nuclear Medicine,<sup>1</sup> Hormonology,<sup>2</sup> Immunology,<sup>3</sup>  
and Hematology,<sup>4</sup> Pasteur Institute of Tunis, Tunisia; Departments  
of Hematology CHU Hedi Chaker Sfax,<sup>5</sup> CHU, Aziza Othmana  
Tunis<sup>6</sup> and CHU Farhat Hached Sousse, Tunisia<sup>7</sup>

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Correspondence: Chokri Maktouf, Institut Pasteur Tunis, BP 74,  
1002, Tunis. E-mail: chokri\_maktouf@yahoo.fr

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