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Biermer Disease: Initial Presentation and Follow-Up of 66 Patients in Internal Medicine Department in Senegal

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Abstract

Pernicious anemia in black people, is little known. Through this study we assess its diagnostic and evolutive aspects, and compare vitamin therapy B12 intramuscular and oral. Sixty six Biermer disease patients followed (January 2000-June 2014) at Internal Medicine Department of Aristide Le Dantec University Teaching Hospital (Senegal) are included. They were 26 men and 46 women (gender ratio: 0.65), who had a mean age of 47.84 years ± 15.25 years. Patients consulted for anemia (65 cases), acquired melanodermia (36 cases), gastrointestinal symptoms (30 cases), peripheral neuropathy (27 cases), venous thrombosis (2 cases), acute depression (1 case). Macrocytosis was observed in 52 cases. The mean hemoglobin in the vitamin B12 intramuscular group (52 patients) or oral group (14 patients) was the inclusion: 6.55 g/dl ± 3.12 g/dl vs 6.52 g/dl ± 2.18 g/dl (p = 0.04); and at day 8 treatment: 8.69 g/dl ± 2.49 g/dl vs 8.85 g/dl ± 1.9 g/dl (p = 0.43). Neurological and vascular presentations are unusual in contrast to macrocytic anemia. Oral administration of vitamin B12, simple and effective should be recommended in country with limited resources.

Keywords

Pernicious Anemia, Intramuscular Vitamin B12, Oral Vitamin B12, Senegal

1. Introduction

Biermer disease or pernicious anemia is a chronic auto-immune disease responsible for a chronic gastritis and a vitamin B12 deficiency, reversible under vitamin B12 therapy which oral administration is validated [1]. It is considered rare in black people and re-

lated literature in sub-Saharan Africa is limited to few case reports [2]-[5]. To our knowledge no publications about practice of oral vitamin therapy B12, is available in sub-Saharan Africa. With this series we propose to describe diagnostic and progression aspects, and to compare outcome on vitamin therapy B12, intramuscular and oral.

2. Patients and Methods

It is a retrospective, descriptive study with analytical outlook conducted upon comprehensive enrollment of medical files of Biermer disease patients followed from 1st January 2000 to 30th June 2014. The study held at Internal Medicine Department of superior referral hospital of Aristide Le Dantec University Teaching Hospital (Senegal) which has consultation, hospitalization and research activities. Our study included 66 files of Biermer disease, onto an annual average of 685 inpatients and 14,871 outpatients at Internal Medicine Department.

The diagnosis of Biermer disease was made in the presence of positive anti-intrinsic factor or anti-parietal cells antibodies, associated or not with vitamin B12 deficiency and atrophic gastritis [1]. Epidemiological, clinical and paraclinical data were analyzed. Bone marrow aspiration and analysis provided precision on the existence of megaloblastosis. Vitamin B12 deficiency was defined by measurements below normal values between 187 and 883 pg/ml.

Positive anti-intrinsic factor and anti-parietal cells antibodies were defined by measurements higher than 1.53 and 40 AU/ml respectively. Upper gastro-intestinal-tract (GIT) endoscopy with systematic antrum and fundusbiopsies and histology revealed gastric atrophy, metaplasia and helicobacter pylori (HP).

Cyanocobalamine is administered intramuscularly (1000 µg once a day for the 1st week, then once a week for a month and once a month for life) or orally (2000 µg per day for 10 days, followed by the same dose once a week for 4 weeks and then once a month for life). Indications for oral administration were: Ongoing anticoagulation, thrombocytopenia below 50,000/mm^3 and difficult access to intramuscular injections. The median follow-up of patients treated with vitamin B12 (oral or intramuscular) was 1135.72, days [8 - 4886 days].

Statistic tests (medium, standard deviation, Student test) were done using Statistical Package for Social Sciences 20 software.

3. Results

The files of 40 women and 26 men (gender ratio: 0.65), with mean age of 47.84 years ± 15.25 were included.

Comorbidities were metrorrhagia (2 cases), hemorrhagic cystitis (1 case) and partial gastrectomy for a benign tumour (1 case), vitiligo (5 cases), type 2 diabetes mellitus, Hashimoto thyroiditis (2 cases) and multiple auto immune disease syndrome (2 cases).

In 28 medical files blood group was specified and it was O (12 cases), A (7 cases), B (7 cases) and AB (2 cases)

Mean diagnostic time was 16 months (6 - 48 months). Presenting symptoms (**Table 1**) were anemia signs (65 cases), palmo-plantar acquired diffuse melanodermia (36

Table 1. Clinical and paraclinical characteristics of the patients of our study.

Clinical signs on diagnosis	n/N = 66	(%)
Anemia manifestations		
Anemic syndrome	40	(60.6)
Hemolytic anemia	13	(19.7)
Anemic heart disease	7	(10.6)
Isolated conjunctiva pallor	5	(7.6)
GIT manifestations		
Epigastric pain	30	(45.5)
glossitis	21	(31.8)
diarrhea	6	(9)
constipation	4	(6)
dysphagia	3	(4.5)
Dermatologic manifestations		
melanodermia	36	(54.5)
Neuropsychiatric manifestations		
polyneuropathy	27	(40.9)
posterior cord syndrom	1	(1.5)
Acute depression	1	(1.5)
Venous manifestations		
Saphenous and femoral thrombophlebitis	1	(1.5)
Portal vein thrombosis incidentally discovered	1	(1.5)
Paraclinical signs	**n/N**	**(%)**
Anemia	65/66	(98.5)
Thrombocytoenia	33/66	(50)
Leukocytopenia	29/66	(43.9)
Pancytopenia	25/66	(37.9)
Bicytopenia	18/66	(27.3)
Thrombocytosis	2/66	(3)
Hyperleukocytosis	1/66	(1.5)
Vitamin B12 deficiency	59/66	(89.39)
Central megaloblastosis	37/47	(88.1)
Positive anti-intrinsic factor antibodies	50/51	(98.03)
Positive anti-parietal cells antibodies	25/36	(69.44)
Atrophic gastritis	34/37	(91.89)
Antrum and pyloric metaplasia	10/37	(27.02)
Helicobacter pylori	2/37	(5.4)

N: Total number of patients who did the test; n: Number of patients with abnormalities; %: Percentage.

cases), GIT signs including Hunter glossitis (21), polyneuropathy (27 cases) which one posterior cord syndrom, acute transient depression (1 case) and deep venous thrombosis (2 cases). The discovery of the disease was incidental in one patient who only had macrocytosis with no anemia (1).

Blood count (BC) (Table 1 & Table 2) revealed anemia (65 cases), macrocytosis (52

Table 2. Blood Count and reticulocyte count: At the beginning of the study and progression according to the administration route of vitamin B12.

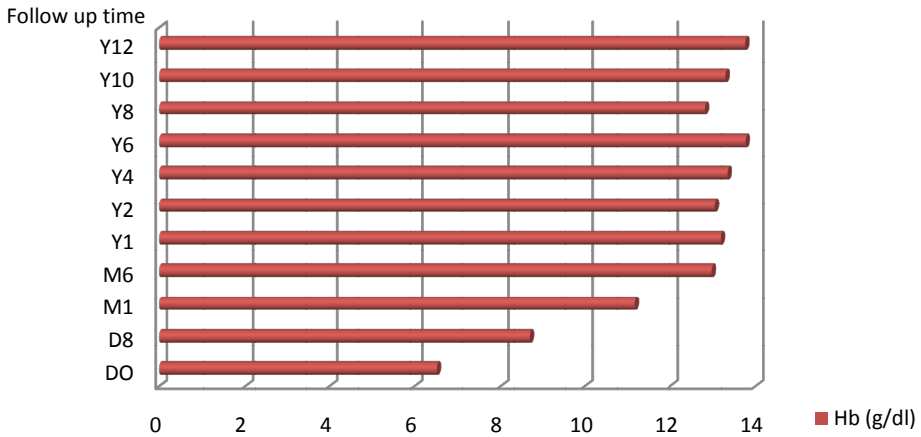
Parameters	Beginning of the study	Mean	SD Extreme	
D0: Hb (g/dl)	6.52	2.93	[1.3 - 15.2]	
MCV (fl)	107.04	11.36	[81 - 131]	
MCTH	34.4	5.04	[22 - 42.06]	
PLT (G/L)	148.31	487.44	[170 - 488]	
WBC (G/L)	4.39	2.17	[1.5 - 15.10]	
Ret. count (G/L)	30.89	29.24	[2 - 98]	
	According to the route of administration of vitamin B12			p¥
	Intramuscular (N = 52)	**(n) Mean SD**	**Oral (N = 14)**	**(n) Mean SD**
D0: Hb (g/dl)	(52) 6.55	3.12	(14) 6.52	2.18	0.43
MCV (fl)	106.06	11.76	110.66	9.21	0.09
Ret. count (G/L)	55.26	29.78	49.29	28.74	0.37
D8: Hb (g/dl)	(52) 8.69	2.49	(14) 8.85	1.9	0.83
MCV (fl)	100.03	10.72	99.53	8.51	0.89
Ret. count(G/L)	104.65	102.78	145.52	87.39	0.27
M1: Hb (g/dl)	(41) 10.83	2.23	(12) 11.81	1.16	0.16
MCV (fl)	94.0	13.34	90.91	6.81	0.18
Ret. count(G/L)	149.58	130.70	212.21	79.71	0.22
M6: Hb (g/dl)	(23) 12.71	1.89	(12) 13.33	1.02	0.96
MCV (fl)	86.02	8.60	86.14	8.28	0.97
Ret count (G/L)	213.76	102.32	297.00	54.76	0.04

N: total number of patients treated, n: number of patients explored; Hb: hemoglobin; MCV: Mean Corpuscular Volume; Ret Count: reticulocyte count; SD: Standard deviation; Mean: Mean value; D0: Day 0 on admission; D8: Day 8; M1: 1st month; M6: 6th month; p¥: Student test.

cases) and hypochromia (4 cases). One patient had isolated macrocytosis at 115fl with hemoglobin of 15.2 g/dl. The mean hemoglobin was 6.52 g/dl ± 2.93 g/dl was below 6 g/dl in 47.7% of patients. BC (Table 1) also revealed thrombocytopenia (39 cases) out of which 7 were below 50 G/L without bleeding, leukocytopenia (28 cases), thrombocytosis at 460 G/L reactive to iron deficiency, and thrombocytosis at 488 G/L associated with leukocytosis at 15.1 G/L in the context of pyelonephritis. There were cytopenias in form of pancytopenia (25 cases) and bicytopenia (18 cases). Reticulocyte count was low in all patients (Table 2). Traces of hemolysis were noted in 18 patients who had mean LDH at 522IU/l [451 - 612 UI/l] and direct serum bilirubin at 21 mg/l [13 - 32 mg/l].

In addition to BC abnormalities, we found megaloblastosis (88.7%), positive anti intrinsic factor (98.03%) and anti parietal cells antibodies (69.40%), atrophic gastritis (91.89%) and HP infection (5.4%) (Table 1).

Overall evolution after intramuscular (52 cases) or oral (14 cases) vitamin therapy B12 is favorable. On day eighth, is observed a mean reticulocytosis crisis of 119.63 G/L ± 97.94 G/L [36 to 466.46 G/L]. Hemoglobin levels is rising during vitamin B12 administration (Figure 1). Hemoglobin levels increased after 6 months in 83.9% of patients



D0 : day on admission ;D8: day eight; M1 : 1st month ; M6: 6th ; month; Y1: 1st year; y2: 2nd year ; Y4: 4th year; Y6: 6th year ; Y8: 8th year; Y10: 10th year ; Y12 : 12th year
Hb : mean of hemoglobin ;

Figure 1. Evolution of the average rate of hemoglobin.

and after 1 year the improvement was at 91.7% of patients.

In analytical study the mean hemoglobin level on vitamin B12 supplements in the intramuscular group versus oral, was on day eight 8.69 ± 2.5 g/dl Vs 8.85 ± 1.9 g/dl (p = 0.43) and after 1 month it was 10.83 ± 2.2 g/dl Vs 11.81 ± 1.1 g/dl (p = 0.16) (**Table 2**). In oral group the reticulocyte count which was at 49.29 G/L initially rose to 297 G/ Lafter 6 months (**Table 2**).

4. Discussion

The available literature on Biermer disease in sub-Saharan Africa is made of limited series.

In 2003, Segbenaet al [2] reported 4 observations and in 2013, Diopet al [3] collected 28 cases over 6 years. To our knowledge, our study is the largest series carried out in Senegal (66 cases) and is the 1st describing oral vitamin B12 therapy.

In our study as well as in other african publications [2]-[5], Biermer disease is common in women in their fifties. Predominant signs on presentation in our study were anemia signs, which also were almost present in de Segbenaet al [2] and Ndiaye *et al.* [4] with respective prevalences of 100% and 80%.

In our study, anemia signs are predominantly made of anemic syndromefar ahead of hemolytic anemia and anemic heart disease. Heart failure as described in our patients is a chronic complication of cardiovascular manifestations common to all vitamin B12 deficiencies as described in almost 50% of cases by Nafil *et al.* [6].

Acquired melanodermia, second presenting sign in our study is also frequently reported in African publications [3] [4]. It is a diffuse homogenous melanodermia with buccal and palmo-plantar predominance secondary to disturbed tyrosine synthesis, this being a melanin precursor [7].

The third diagnostic condition in our study was GIT signs with atypical epigastric

pain, followed by Hunter glossitis. This one is more specific of Biermer disease and was noted in 78.57% of patients in Diop *et al.* series [3].

The least observed manifestation in our patients was deep venous thrombosis. As a comparison Zulfiquar *et al.* [8] and Diop *et al.* [3] respectively reported 10 and 2 observations.

Beside thrombosis, acute depression and combined sclerosis of the bone marrow are rare in our study (1 case) like in the literature [4] [8] [9].

Main BC abnormalities were macrocytic anemia followed by thrombocytopenia and neutropenia both in our patients and in Song and al series [10] who reported 65% of thrombocytopenia and 45.5% of leucopenia. However some authors [11] didn't note any difference in the prevalence of leukocytopenia and thrombocytopenia. These cytopenias are more combined into pancytopenia orbicytopenia [3] [4] [8]. Early diagnosis at the macrocytosis stage before cytopenia is rare [5], we only hadone observation. Beside the frequent macrocytosis, normocytosis and hypochromia are not exceptional [3] [8]. They are due to additional factors like iron deficiency in bleeding of our patients for example or other comorbidities like association with beta thalassemia and Plummer Vinson [3].

Characteristic bone marrow aspirate findings in our study were the high frequency of megaloblastosis, coinciding with results of de Segbena *et al.* [2] (100%) and Wun Chan *et al.* [9] (95%).

Positive anti-intrinsic factor antibody which is more specific of the disease [3] [9], was almost constantly present in our study.

Prevalence of atrophic gastritis was high unlike HP surinfection which was rare. Similar findings in this regard were also obtained by Wun Chun *et al.* [9] who published cases of HPsurinfection par HP in 109 Biermer disease patients who underwend upper GIT endoscopy with biopsies.

On therapeutic aspect, hematologic abnormalities are reversible with vitamin B12 treatment, more frequently administered intramuscularly in our study and in the literature [1] [4]. Song *et al.* [10] noted that 94.3% of anemia regressed after 3 months treatment with vitamin B12.

Oral route of administration is effective and is indicated in case of severe thrombocytopenia or anticoagulation treatment [1]. In addition therapeutic compliance is better obtained with oral administration in patients with difficult access to health care. In analytical study we noted that oral vitamin B12 allowed cytopenia regression by day eight and reticulocytosis was statistically significant after 6 months. The absence of statistical significance of some of our tests was a bias due to the limited number our series enrolled.

5. Conclusion

Macrocytic anemia and acquired melanodermia are frequently revealing sign of Biermer disease, in contrast to neuropyschiatric and vascular manifestations. Oral route of vitamin B12 administration, simple and equally effective should be strongly promoted

in sub-Saharan Africa regions with limited resources.

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