

Profile of Biermer's Disease at the Medical Clinic II Abass Ndao Hospital Center: About 57 Colliged Cases

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Abstract

Introduction: Biermer's disease is an autoimmune cause of anemia characterized by malabsorption of vitamin B12. It is often accompanied by other autoimmune pathologies. The objective was to study its profile in patients followed in the internal medicine department of the Abass Ndao hospital center.

Methods: This was a retrospective and descriptive study of patients followed for Biermer's disease from January 1, 2014 to December 31, 2019 (5 years).

Results: 57 cases were collected, an incidence of 5.4 in the internal medicine department. The sex ratio was 0.58, an average age of 56.4 years. The circumstances of discovery were dominated by anemic syndrome (87.7%), dermatological (33.3%), digestive (29.8%), neurological (20%) pathologies. The specific signs to Biermer's disease were digestive manifestations in 70.2% (including 30% Hunter's glossitis), neurological manifestations in 36.8% (including 17.5% paresthesias), palmoplantar melanoderma in 68.4%. The mean hemoglobin level was 6.8 g/dL with a mean corpuscular volume of 110.7 fl. The myelogram reported megaloblastosis in 100% of the cases. The mean serum vitamin B12 level was 100 pg/ml. The anti-intrinsic factor antibody assay performed in 50 patients was positive in all cases. Upper digestive endoscopy showed an aspect of fundic atrophy in 69%. Histology showed intestinal metaplasia in 2 patients. An autoimmune disease was associated in 21% of cases. All patients had received treatment with vitamin B12 (51 patients took intramuscularly and 6 oral treatment). The course was favorable in all cases with a complete correction of the anemia. **Conclusion:** Biermer's disease is a reality in Senegal. Its clinical and biological characteristics can be superim-

posed on the data in the literature. His prognosis under treatment is good whatever the route of administration of vitamin B12.

Keywords

Biermer, Autoimmune Disease, Vitamin B12, Dakar

1. Introduction

Biermer's disease (formerly known as pernicious anemia) is an autoimmune atrophic gastritis, predominantly fundic, responsible for a malabsorption of vitamin B12. It is characterized immunologically by the presence of anti-intrinsic factor antibodies and/or anti-parietal cells antibodies. Its prevalence is 0.1% in the general population and 1.9% in subjects over 60 years of age. It accounts for 50% of the etiologies of vitamin B12 deficiency in adults [1]. It most often manifests as a neuro-anemic syndrome associated with digestive signs, notably Hunter's glossitis and melanoderma. It is often associated with other autoimmune disorders (vitiligo, dysthyroidism, autoimmune adrenal insufficiency, Sjögren syndrome) [2] [3]. Its treatment is based on the administration of vitamin B12 for life by the parenteral route [1] or oral [4]. Biermer's disease remains insufficiently described in Senegal. In Senegal, an old retrospective study carried out in 2008 focused on this pathology but did not assess the impact of oral treatment. The objective of this study will be therefore to study the clinical epidemiological profiles but also the associated comorbidities and the course of treatment in patients followed at the Abass Ndao Hospital Center.

2. Patients and Methods

This was a retrospective, descriptive study of the cases of Biermer's disease collected over a period of 05 years (from January 1, 2014 to December 31, 2019). We included in the study any patient for whom the diagnosis of Biermer's disease was confirmed. Apart from clinical manifestations, the confirmation of Biermer's disease in our series was carried out on a bundle of arguments. These were: the existence of a macrocytic type anemia (mean corpuscular volume > 100 fl) and/or a decrease in serum vitamin B12 levels (vitamin B12 less than 130 ng/l) and/or megaloblastosis in the medullogram and/or a positivity of intrinsic anti-factor antibodies and/or the presence of endoscopic or histological signs of atrophic gastritis. Incomplete records (hemogram, serum vitamin B12, anti-intrinsic factor antibody, esogastroduodenal fibroscopy, medullogram) were not included. The data were collected on a pre-established survey sheet and were also collected from patient medical records. The parameters necessary for the study were:

- Socio-demographic data: age, sex, existence of an associated autoimmune disease;

- Clinical data: circumstance of discovery, anemic syndrome, digestive, dermatological, neuropsychic signs.

We also took into account the biological data: hemogram, myelogram, serum folic acid, plasma ferritin, serum vitamin B12, antibodies against intrinsic factor, antibodies against parietal cells. The reference values were 130 - 800 ng/l for vitamin B12, 150 - 450 ug/l for folic acid, 18 - 160 ng/l in men and 7 - 160 ng/l in women for ferritin. The results of upper gastrointestinal endoscopy as well as those of histology were also collected. Apart from the full clinical examination, an exploration of associated pathologies, especially autoimmune, was made either directly (specific antibodies in the event of signs of orientation) or indirectly by the determination of calcemia, glycemia, TSH us, cortisol, protidemia.

Therapeutically, the dosage and method of administration of vitamin B12 were noted. It consisted of the administration of vitamin B12 in the form of hydroxycobalamin.

Two protocols have been established:

- Intramuscularly: 1000 µg per day for one week, then 1000 µg per week for one month, then 1000 µg once per month for life;
- Orally: 2000 µg per day for one week then 2000 µg per week for one month; then 2000 µg per os once a month for life.

The adjuvant treatments were an iso-group iso-rhesus blood transfusion in case of poorly tolerated anemia, iron supplementation for iron deficiency, eradicator treatment for *Helicobacter pylori*.

The evolution under treatment was evaluated on the erythrocyte response after 7 days of treatment (the erythrocyte crisis was retained on an increase in the reticulocyte level greater than 10 times normal), on the correction of anemia over 3 months, the state of neurological, gastric manifestations and death.

The results were captured and analyzed using an electronic questionnaire developed with SPSS 24.0 software. This software was used to calculate frequencies, averages and standard deviations.

3. Results

3.1. Epidemiological Data

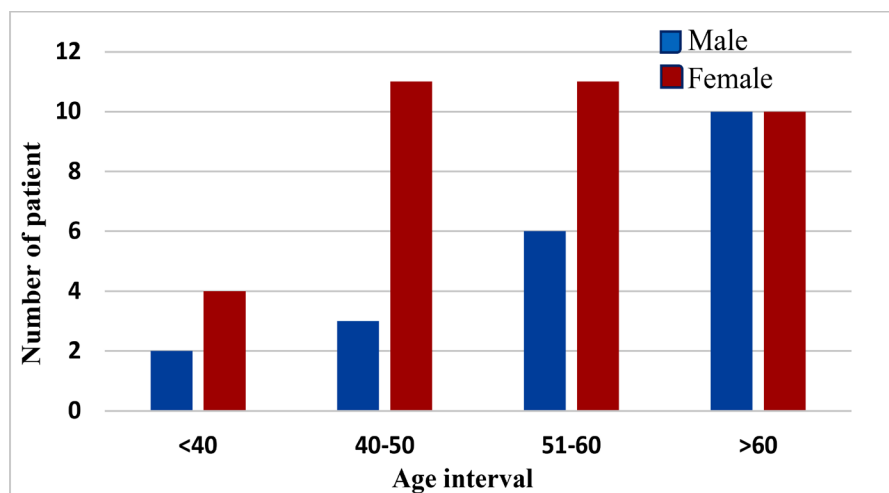
We included 57 patients among 1044 patients followed in internal medicine (consultation and hospitalization) during the study period, an incidence of 5.46%. These were 21 men and 36 women, for a sex ratio of 0.58. The average age of the patients was 54.6 ± 13 years (extremes of 27 and 80 years). It was on average 53 years for women and 59.2 years for men (**Table 1**). The most represented age group for women was 40 - 60 years old (61.1%) and that of men over 60 years old (47.6%). **Figure 1** shows the distribution of age groups by gender.

3.2. Clinical Data

The average delay of consultation was 15 months. The reasons for consultation were dominated by symptoms of anemia in 87.7%, followed by dermatological

Table 1. Epidemiological profile of patients by gender.

Data		Frequency (%)
Effectives		57
Women		36 (61.1%)
Men		21 (47.6%)
Sex ratio		0.58%
Average age of the population		54.6 ± 13 years
Average age by gender	Female	53 years
	Male	59.2 years
Most represented age group	Woman	40 - 60 years (61.1%)
	Man	More of 60 years (47.6%)

**Figure 1.** Distribution of age groups by gender.

(33.3%), digestive (29.8%) and neurological (20%) manifestations.

In terms of the signs specific to Biermer's disease, palmoplantar melanoderma was noted in 39 patients (68.4%) (**Figure 2**). Anemic syndrome was found in 50 patients (87.7% including pallor in 82.5%, jaundice in 26.3% and anorganic systolic murmur in 14%). Anemic syndrome was poorly tolerated in 35 patients (61.4%) who required a blood transfusion. Digestive signs were present in 44 patients (70.2%) dominated by Hunter's glossitis (29.8%) (**Figure 3**) and chronic epigastralgia (25%). Neurological signs were present in 21 patients (36.8% including limb paresthesia in all cases, combined sclerosis syndrome in 10.5%). **Table 2** summarizes the clinical signs found in our patients.

3.3. Paraclinical Data

The hemogram found anemia in 93% of patients (n = 53). The average hemoglobin level was 6.8 g/dl (extremes of 1.8 and 15). It was less than 5 g/dl in 33.3% and between 5 and 8 g/dl in 24.6%. The mean corpuscular volume (MCV) was 110 fl (extremes of 90 and 140). Anemia was predominantly macrocytic in 77%,

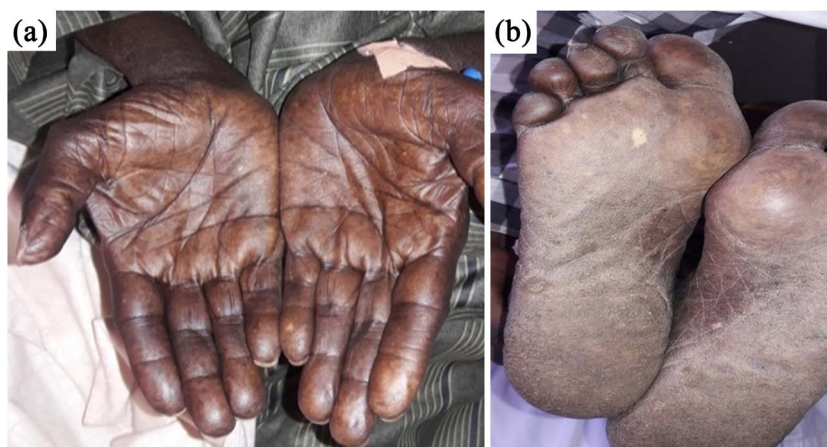


Figure 2. Palmo (a) plantar (b) melanoderma related to Biermer's disease.

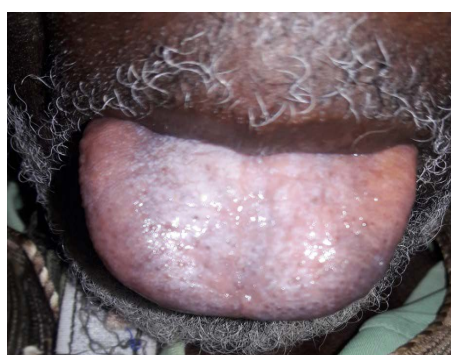


Figure 3. Hunter's glossitis (Abass Ndao Medical Clinic).

Table 2. Clinical characteristics of patients.

Clinical signs		Effectives	Percentage
Anemic syndrome	Skin and mucous pallor	47	82.4%
	Anorganic systolic breath	8	14%
	Tachycardia	53	93%
	Dyspnea exertional	35	61.4%
Digestive manifestations	Hunter glossitis	17	29.8%
	Transit disorders	17	29.8%
	Epigastralgia	12	21%
Neurological manifestations	Combined spinal sclerosis	6	10.5%
	Sensitive neuropathy	5	8.8%
	Isolated paraesthesia	10	17.5%
Dermatological signs	Palmoplantar melanoderma	39	68.4%

normocytic in 23%. Bi-cytopenia was noted in 23 patients or 40% of cases and pancytopenia in 17 patients or 30% of patients. The dosage of serum vitamin B12 was done in 48 patients or 85.7%. Vitamin B12 deficiency was noted in all patients with an average serum level of 100 pg/ml (extremes of 23 and 156). Iron

deficiency (low serum ferritin levels) was associated in 14% of the cases. Anti-intrinsic factor antibodies were produced in 40 patients (71.4%). They were positive in all cases. Functional renal failure was found in 30 cases (52.6%).

The myelogram, performed in 35 patients, found megaloblastosis in all patients. Esogastroduodenal fibroscopy (F.O.G.D.) was performed in 52 patients (91%). It was associated with a biopsy in 11 patients or 11%. It showed atrophic gastritis in 69% of patients (n = 34), intestinal metaplasia in 2 patients (3.5%). *Helicobacter Pylori* was found in 3.5% of cases (n = 2).

3.4. Therapeutic Data

Treatment with vitamin B12 was prescribed in all patients. The intramuscular route was used in 41 patients and the oral route in 16 patients. Blood transfusion was required in 35 patients (61.4%). Eight patients with associated iron deficiency received iron supplementation and 3 patients received *Helicobacter pylori* eradication therapy. Normalization of hemoglobin level was observed in all patients after an average of 03 months of treatment. The course was marked by a reticulocytic crisis on the 8th day of treatment in all patients.

3.5. Associated Pathologies

Organ-specific autoimmune disease was associated in 12 patients (21% including 7% autoimmune dysthyroidism, 3.5% type 1 diabetes, 5.3% vitiligo damage and 1.7% systemic lupus).

4. Discussion

It was a retrospective, descriptive study of the profile of Biermer's disease. It presented limits because the paraclinical explorations, often necessary for the diagnosis, were not always accessible. The exploration prices were on average 87,000 fcfa for vitamin B12 + antibodies against intrinsic factors, 12,000 fcfa for the medullogram and 30,000 fcfa for digestive endoscopy. As a result, many patients did not carry out all of the necessary investigations.

4.1. Epidemiological Data

The female prevalence and the average age noted in our series were superimposable on the data of the literature [5] [6] and comparable to the gender profile of autoimmune diseases. Biermer's disease is described as rare before 30 years of age, with a frequency which then increases, reaching a peak around 60 years of age [7]. The average delay of consultation was 15 months. This long delay is partly linked to the chronic and asymptomatic nature of the disease.

4.2. Clinical Data

Anemia is almost constant during Biermer's disease and is the main manifestation reported in Sub-Saharan Africa [5] [6]. In the series by Ndiaye *et al.* [6], the revealing manifestations were dominated by anemia in 100% of the cases, fol-

lowed by epigastralgia (61.5%), glossitis (23.1%), transit disorders (15.3%). Neurological (53%) and dermatological (42.3%) manifestations were also reported. In our series, Hunter's glossitis was the most suggestive sign of the disease. Regarding the neurological manifestations, there were mainly paresthesias of the lower limbs (17.5% of cases). According to the literature, this peripheral sensory neuropathy is quite frequent and constitutes the first neurological manifestation of Biermer's disease [8]. Furthermore, the combined degeneration of the spinal cord remains the classic neurological picture during this disease. According to Ndiaye *et al.* [6], it represents 20% to 30% of Biermer's diseases with neurological presentation. We found 10% of combined sclerosis of the spinal cord. Palmoplantar melanoderma found in 68.4% of our patients remains less described in the literature. It is more frequent in black subjects than in leukoderms [6]. The study by Ndiaye *et al.* [6] reported 42.3% of cases.

4.3. Paraclinical Data

On the biological level, the anemia found in 93%, remains frequently reported [7] [8] [9]. However, Biermer's disease can present without anemia [6]. In the series of Lindenbaum *et al.* [10] and Federici *et al.* [3], the hemoglobin level was normal in 24% and 28% respectively. Analysis of hematimetric constants noted macrocytosis more frequently (77%). Conventionally, Biermer's disease manifests with macrocytosis [6] [7] [11]. However, the mean corpuscular volume can also be normal in the case of Biermer's disease even in the absence of associated pathology [12]. Achlorydria can be the essential determinant through an associated iron deficiency. Besides anemia, leukopenia or thrombocytopenia are sometimes seen during this disease. In the Maktouf *et al.* [13] cohort, 48% of cases had thrombocytopenia. In the literature, several authors have reported cases of pancytopenia [3] [6] [13] [14]. Besides the medullary richness, the existence of megaloblasts, observed in 100% of our subjects, was constantly reported by the literature [3] [6] [8]. The positivity of anti-intrinsic factor antibodies remains specific at 98%. These antibodies can however be found in 2 to 5% of healthy subjects, as well as in 1st grade parents of an affected subject. [15]. However, the absence of anti-intrinsic factor antibodies and anti-parietal cell gastric antibodies does not rule out this diagnosis, since these immunological abnormalities are absent in approximately 30% of cases during authentic Biermer disease [16].

Histologically, the rate of atrophic gastritis found at 69% agrees with the literature [6] [14]. It is an almost constant diagnostic criterion reported with a high frequency in the majority of published studies. However, Biermer anemia can be observed outside of any gastric atrophy [5] [6]. A triggering role for *Helicobacter pylori* in the autoimmune process has been suggested [17].

4.4. Therapeutic Data

The parenteral route remains the preference in all African series [9] [12] [14]. However, recent studies have opened several perspectives by suggesting the in-

terest of the oral route or even the nasal route [4] [18]. There is no consensus on the dosage and timing of vitamin B12 during Biermer's disease. The same is true for the use of oral vitamin therapy. Many comparative therapeutic trials have confirmed the efficacy of vitamin B12 administered orally, in particular with the studies of Troilo *et al.* [19] and Kaltenbach *et al.* [20]. In fact, the first team to evaluate the effectiveness of vitamin B12 by the oral route, in Biermer's disease and para biermerian, noted a significant increase in the serum concentration of vitamin B12 on average by 161.6 ± 79 pg/ml in the maldigestion group ($p < 0.00005$) and 136.7 ± 67.4 pg/ml in the group of patients with Biermer's disease ($p < 0.0001$) [20]. Symptomatic treatment was mainly iso-rhesus iso-group blood transfusion in 61.4%. This rate was almost similar to that of Wun Chan *et al.* [8] which reported 76%.

The evolution marked by an improvement in the anemic syndrome and neurological signs was matching with the data in the literature [21] [22]. In the Andrès *et al.* [23] series, the average hemoglobin level increased from 6.2 to 12.4 g/l and the mean corpuscular volume from 103.5 to 91.2 fl in 4 months.

In our study, we observed an association with other autoimmune diseases in 12 patients. In the Tunisian studies of Maktouf *et al.* [8] and Achat *et al.* [24], it was found that mainly autoimmune thyropathies are in 23.4% and 57% respectively.

5. Conclusion

In Biermer's disease, the majority profile of the elderly female subject remains demonstrated. There is a clinical polymorphism dominated by anemia, Hunter's glossitis. The macrocytic profile dominates, however some chronic cases were revealed by normocytosis. The positive immunological assessment in our patients confirms our diagnoses. Upper gastrointestinal endoscopy remains crucial in the identification of atrophic gastritis. Because of its autoimmune nature, a systematic search for another associated autoimmune pathology is required. Therapeutically, all our patients have benefited from lifelong B12 vitamin therapy mainly via the intramuscular route. At the end of this study, it would be important to evoke Biermer's disease before any macrocytosis, even isolated, in order to reduce the diagnostic delay, to use the alternative route to injectable treatment which is also effective, to make additional examinations accessible including immunological examinations for early diagnosis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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