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Biermer Disease in an Unusual Neurological Presentation without Anemia: A Case Report

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Abstract

Background: Biermer disease is a megaloblastic disease caused by vitamin B12 deficiency. It is a rare clinical entity especially in subsahara Africa. **Case presentation:** We report the case of a 45 years old female patient who consulted for a one month history of generalised muscle cramps, weakness and numbness of all four limbs. Physical examination was relevant for a poor gait, poor coordination of both upper and lower limbs, a positive Romberg sign, normal muscle tone in all four limbs, reduced pallesthesia and deep tendon reflexes, abolished plantar reflexes. Paraclinical investigations revealed macrocytosis without anemia, a low cyanocobalamin (vitamin B_{12}) level with a normal folic acid level, an atrophic corporeofundic mucosa which upon pathological analysis revealed a chronic atrophic gastritis with no *Helicobacter pylori* infection. Anti-intrinsic factor antibodies were positive while anti parietal cells antibodies were negative. The diagnosis of Biermer disease was considered and the patient did well on vitamin B_{12} supplementation. **Conclusion:** Though a rare disease, Biermer disease should be considered in a patient who consults for polyneuropathy even in the absence of anemia.

Keywords

Biermer Disease, Pernicious Anemia, Autoimmune Disease, Atrophic Gastritis, Vitamin B12 Deficiency, Cameroon

1. Introduction

Biermer disease, or pernicious anemia is a megaloblastic anemia caused by the

deficiency of vitamin B_{12} (cobalamin) which not only plays a vital role in blood cells production (as it is important in DNA systhesis), but also in neurological fonctions. It is an auto-immune disease of unknown etiology which results in the production of auto-antibodies against intrinsic factor (IF), a glycoprotein produced by gastric parietal cells, which facilitate vitamin B_{12} absorption in the terminal ileum. It is a rare disease. We are reporting the case of a 45 years old patient with an atypical presentation of Biermer disease in Ebolowa, South of Cameroon.

2. Case Presentation

We are reporting the case of a 45 years old female patient, married, mother of one child, teacher by profession living at Ebolowa, who consulted for numbness of all four limbs, generalised muscle cramps, weakness, which had been evolving for a month prior to consultation for which she had been on Calcium and Magnesium supplementations with no improvement.

Her past medical record is relevant for iron supplementation and traditional medicine three months prior to consultation in the setting of epigastric crampy pain and vomiting. No prior investigation was carried out. She does not smoke and rarely drinks alcohol. She is not on a vegeterian diet. There is no drug allergy. Her gynaecological history is relevant for secondary infertility and a right ovarian cystectomy. No other chronic ailment has been reported.

Systemic enquiry revealed a six weeks history of poor gait with generalised muscle cramps, numbness of all four limbs, and blurred vision. There was no head ache, no cough, no fever, no sign of lower urinary tract infection. Her bowel movements were satisfactory, but complained of crampy epigastric pain.

Physical examination revealed a healthy looking patient. There was no palor nor jaundice. The Blood pressure was 130/84mmHg with a pulse rate of 101/minute.

Neurological examination revealed a poor gait, with poor coordination of both upper and lower limbs. The Romberg sign was present. There was no muscle waisting. The muscle tone was normal in all four limbs. Pallesthesia and deep tendon reflexes were reduced. The plantar reflexes were abolished.

The digestive, cardiovascular and respiratory systems were unremarkable.

The following paraclinical investigations were conducted. A full blood count revealed a hemoglobin level of 12.2 g/gl with a mean corpuscular volume of 103.6 fl (**Table 1**). Blood electrolytes were normal bet for mild hypocalcemia (77.1 mg/l). Serum cyanocobalamin (vitamin B_{12}) was less than 74 pmol/L (normal range: 145 - 569 pmol/L), with a normal folic acid level. An eosogastroduodenoscopy revealed an atrophic corporeofundic mucosa (**Figure 1**). Pathological analysis of fundal biopsies showed chronic moderate atrophic gastritis, not associated to *H. pylori*. Anti-Intrinsic factor antibodies were positive (9.72 U/ml) while anti parietal cells antibodies were negative. Fasting blood glucose and thyroid enzymes (TSH and T_3/T_4) were all normal.

The diagnosis of pernicious anemia is made when patients have a low vitamin B_{12} level and positive intrinsic factor antibodies or parietal cells antibodies on

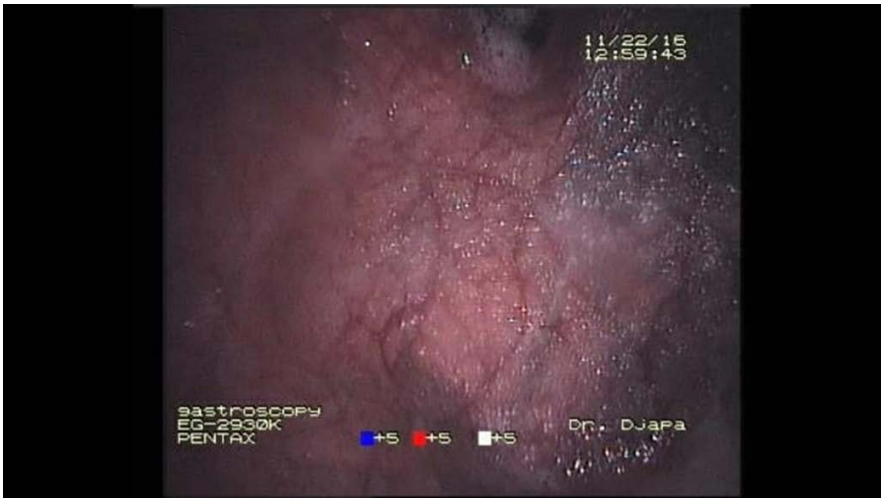

Figure 1. The fundal atrophy.

Table 1. The full blood count results of the patient.

	At diagnosis	At year 1 on Treatment
Hemoglobin	12.2 g/dl	11.9 g/dl
MCV	103.6 fl	86.1 fl
Red blood cells	$3.9 \times 10^6/mm^3$	$4.1 \times 10^6/mm^3$
White blood cells	$2700/mm^3$	$3700/mm^3$
Platelets	$174{,}000/mm^3$	$124{,}000/mm^3$

one hand or low vitamin B_{12} level and the presence of an atrophic gastric mucosa, establishing the autoimmune nature of the disease. It was thus considered and she was started on intramuscular hydroxycobalamin (vitamin B_{12}) supplementation, initially 1 mg/day for two months, then weekly for a month before giving 1 mg/month. This was marked clinically by the persistence of neurological findings by the end of the first week (with no worsening). We started observing a regression of neurological findings by the seventh week starting with paresthesia and numbness. By the end of the third month, her gait was considerably improved as she could walk unassisted. Her vitamin B_{12} level rose to 564 pmol/L by the end of the fourth month. Resumption of professional activities took place at the end of the sixth month. A full blood count done six months later showed a normal mean corpuscular volume (Table 1).

3. Discussion

Biermer disease is a rare blood disorder characterized by the inability of the body to properly utilize vitamin B_{12} which is essential in hematopoiesis and the development of the nervous system. Most cases result from the lack of the gastric protein known as intrinsic factor (IF), without which vitamin B_{12} cannot be absorbed. It accounts for about 50% of the etiologies of vitamin B_{12} in adults [1]. There is growing evidence that the disease is more frequent among blacks [2] [3]

[4] [5]. In most Africa publications, Biermer disease is common in women in their fifties. Our patient is female aged 45 years of age at presentation. The mean age of patients ranges from 59 to 62 years. It is more common in people with African or European ancestry than in those with Asian ancestry. The highest prevalence is seen in northern Europeans, especially those in the UK and Scandinavian countries [6] [7].

Anemia in many case reports and series all over the world is the predominant sign at presentation, with a hemoglobin level generally less than 10 g/dl [2] [3] [8] [9]. Patients generally present both hypoxic and compensatory signs. In our patient however, neurological manifestations were the predominant clinical features, with a hemoglobin level of 12.2 g/dl and macrocytosis (MCV of 103.6 fl) at presentation. It will be difficult to ascertain the absence of anemia before presentation as she had been on iron supplementation 3 months prior to consultation. As a matter of facts, in Biermer's disease, iron deficiency anemia is usually present as a result of achlorhydria secondary to chronic atrophic gastritis.

Cases of overt neurological manifestations without anemia though infrequent have been reported in vitamin B_{12} deficiency. As a matter of facts, anemia or hematological impairments usually start early and preceed neuropsychiatric manifestations of which delayed treatment may lead to permanent disabilities [10] [11] [12] [13] [14]. Neuropsychiatric manifestations are known but less frequent especially early in the disease process. Neurological abnormalities seen in pernicious anemia are a result of vitamin B_{12} deficiency. They are seen in 4% to 50% of vitamin B_{12} deficiency. They could be isolated or be the first manifestations of vitamine deficiency and even occur without hematological or gastrointestinal manifestations. It may affect both the central (brain, spinal cord and optic nerve) and the peripheral nervous system. Demyelination is the initial finding, which progresses to axoval degeneration and neuronal death if left untreated [15]. The most common neurologic findings are symmetric paresthesias or numbness and gait problems. The appearance of motor symptoms is indicative of subacute combined degeneration involving the dorsal and lateral spinal columns. Our patient had severe vitamin B_{12} deficiency and presented with marked neurological manifestations including poor gait, bilateral paresthesia and numbness, bilaterally indifferent plantar response, the presence of the Romberg sign and blurred vision, all of which completely resolved on vitamin B_{12} supplementation. In one recent senegalese series, Seynabou *et al.* reported a prevalence of peripheral neuropathy of 40.9%.

In humans, vitamin B_{12} is needed as a cofactor for two reactions: methylcobalamin is the cofactor for the cytoplasmic enzyme, methionine synthase, while adenosylcobalamin is the cofactor for the mitochondrial enzyme, methylmalonyl coenzyme A mutase. Hence, vitamin B_{12} deficiency results in the accumulation of homocysteine and methylmalonic acid. Cobalamin is known to be essential for DNA synthesis, haematopoiesis and myelination [16] [17] [18]. Given the extreme low level of vitamin B_{12} in our patient, it was not necessary to check for methylmalonic acid and homocysteine levels [19].

Patients with Biermer disease have been shown to have two types of antibodies, parietal cells antibodies and intrinsic factor antibodies. The immune response is directed against the gastric H/K-ATPase which accounts for the associated achlorhydria resulting in iron-deficiency, a situation which generally precedes the onset of vitamin B_{12} deficiency by years [20].

The diagnosis of pernicious anemia is made when patients have a low vitamin B_{12} level and positive intrinsic factor antibodies or parietal cells antibodies on one hand or low vitamin B_{12} level and the presence of an atrophic gastric mucosa, establishing the autoimmune nature of the disease. Our patient had positive anti-intrinsic factors antibodies. It has been shown in many studies to be more specific of PA than anti parietal cells antibodies. Seynabou *et al.* reported 98.5% prevalence in their series [2]. In the same vein, an esogastroduodenoscopy revealed a severely atrophic fundal mucosa (picture). Gastric biopsies carried out as per the Sydney system upon pathological analysis revealed chronic moderately active atrophic gastritis of the body of the stomach which upon immunostaining was *Helicobacter pylori negative*.

Biermer disease correlates with other autoimmune diseases such as thyroiditis and type-1 diabetes mellitus [1]. Our patient had normal thyroid hormone levels and diabetes was ruled out.

The diagnosis of pernicious anemia was considered and the patient started on vitamin B_{12} supplementation. Various therapeutic options do exist, including the intramuscular route, intranasal and the oral routes. There is growing evidence that the oral route is an acceptable alternative to intramuscular injections [2]. However, it is established that in case of neurological manifestations, the route of choice is IM. Our patient was thus started on daily IM administration of 1mg of Hydroxycobalamin for two month, followed by weekly injections for a month and presently is receiving 1mg of hydroxycobalamin monthly.

4. Limits of the Presentation

In the management of our patient, though the diagnostic criteria of Biermer's disease were met, certain investigations could not however be carried out such as blood smear, myelogram and neurophysiological studies.

5. Conclusion

We are reporting one of the first cases of Biermer's disease in Cameroon. Vitamin B_{12} deficiency though commonly associated with hematological manifestations like macrocytic anemia, could rarely present with predominant neurological manifestations in the absence of anemia. Diffuse bilateral polyneuropathy in a patient should prompt the search of vitamin B_{12} deficiency and Biermer disease.

Conflicts of Interest

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

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