ISSN: 2634 - 680X

Journal of Clinical Case Studies Reviews & Reports

SCIENTIFIC Research and Community

Case Report

Open Access

Bisalbuminemias Caused by Betalactamine Antibiotic and Syndrome Nephrotic: Case Report

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ABSTRACT

Bisalbuminemia is a rare qualitative anomaly, it is hereditary or acquired, transient and physiopathology remains a little unknown, characterized by the occurrence of bicuspid electrophoretic pattern in the albumin fraction detected on serum electrophoresis. These albumin mutants also called alloalbumins either have decreased mobility (slow type variants) or increased electrophoretic mobility (fast type variants).

Case Presentation: The study presents 6 cases of bisalbuminemias collected on 2083 serum protein electrophoresis carried out at the laboratory of biochemistry of CHU Ibn Rochd of Casablanca over a spread period of one year (2018).

Conclusions: The results of serum protein electrophoresis of 6 reported cases showed bisalbuminemias which are all of acquired and transient type, of which 3 cases are related to the drug intake of betalactamine antibiotic and the other 3 are related to the syndrome nephrotic.

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Received: March 06, 2024; **Accepted:** March 13, 2024; **Published:** March 20, 2024

Keywords: Bisalbuminemia, Serum Protein Electrophoresis, Betalactamine Antibiotic, Syndrome Nephrotic

Introduction

Bisalbuminemia or alloalbuminemia described for the first time by Scheurlen [1]. It is an anomaly characterized by resolution of the albumin fractions on serum protein electrophoresis [2]. These two fractions can be equal or unequal [3]. The tumbling of albumin is manifested by the presence in the same individual two types of albumin with different electrophoretic mobility, a normal plasma albumin and an albumin modified, bisalbumin [4]. This alloalbuminemia is a very rare case with a frequency of 1/300 to 1/3000 [5]. Bis albuminemia does not result in any hyper protein or hypo protein [6]. It is acquired or hereditary.

Hereditary bisalbuminemia is a rare genetic disorder randomly revealed, it is found in several members from the same family [7]. It is permanent and of codominant autosomal transmission [8]. According, to authors more than 100 albumin variants have been found so far [9]. In addition, the frequency of hereditary bisalbuminemia depends on certain factors namely race, nationality and place of residence. Native American Indians present a high incidence of the anomaly [10]. However, in Europe, hereditary bisalbuminemia is relatively rare between 1/1,000and 1/10,000 of the study population [11]. In Greece, only one case of hereditary bis albuminemia has been reported so far [12]. Similarly, in Morocco, a genetic type of bis albuminemia was identified of a family of Sephardic Jews from Kénitra (Morocco) [13]. This bis albuminemia has no serious consequence, or has an affinity which can affect certain hormones, ions metals, fatty acids and drugs, causing a remarkable rise in blood levels, his diagnosis is necessary for the biologist and the clinician in order to provide recent data on the evolution of proteins and the clinical approach [5]. This information does not add any diagnostic contribution; however the knowledge of a hereditary and permanent bisalbuminemia is very important for the biologist for a good orientation of the patient [14].

The level of the variant is lower or almost the same as normal albumin. And maybe faster than the fraction normal, but most often it is slow [1]. Acquired or transient bisalbuminemia is the result of the modification part of the albumin structure. There are three well-known main causes resulting from acquired bis albuminemia: adhesion of albumin with antibiotics, during pancreatitis and binding with certain immunoglobulins monoclonal [15-17]. Acquired bis albuminemia may explain when amylase in ascitic fluid diagnosed as pancreatitis acute in 93% of cases the level of amylase is increased during pancreatitis [1,18]. Similarly, after breaking of a pancreatic cyst, pancreatic enzymes digest a portion of albumin, resulting in modified albumin [19]. A another study showed bis albuminemia during a pancreaticoperitoneal fistula during acute pancreatitis or chronic [20]. The identification of bis albuminemia on a qualitative electrophoretic tracing after having ruled out drug or hereditary etiopathies, confirms bis albuminemia of pancreatic origin. Bisalbuminemia of pancreatic origin is transient disappears just after recovery from pancreatitis

[21]. Similarly, more than forty cases related to bisalbuminemia pancreatitis have been reported so far.

Regarding, drug-induced bisalbuminemia, appears during treatment with antibiotics after 3 to 8 days and it disappears just after a few days of stopping this drug, this qualitative aspect of bisalbuminemia is identified for a long time, due to the strong binding of beta-lactam with albumin and by fixing the carbamyl of the cycle beta-lactam on albumin [22]. In addition, bis albuminemia is often associated with drug overdose during a long-term treatment with antibiotics, especially in nephrotic subjects [23]. Indeed, beta-lactams is the only drug that causes bisalbuminemia [3].

Bis albuminemia can also be observed in myeloma due to the binding of an immunoglobulin complexed with albumin, usually IgA, and very rarely IgM [3,24].

Some literatures have revealed transient bisalbuminemias, of unusual causes in subjects with sarcoidosis, Alzheimer's disease or chronic kidney failure [25]. In addition, bisalbuminemia is remarkable of a hyper-alpha-feto-protein; AFP migrates into the albumin fraction due to the resemblance functional and structural with albumin [19]. A study has identified bisalbuminemia during the pulmonary neoplasia and liver metastasis [18]. And during liver metastases and digestive adenocarcinoma [26].

Indeed, bisalbuminemia has become more detectable in our laboratory thanks to capillary electrophoresis, knowing that this anomaly was overlooked by conventional electrophoresis [27].

Recently, bisalbuminemia has become a subject of more advanced research, since it has allowed the more precise study human albumin and its variants, these variants can be used as therapy against cancer cells [28].

As cited above in the literature, several pathological cases can be associated with bisalbuminemia. So, are these associations linked by a well-defined physiological mechanism or just a coincidence?

The purpose of this work is to identify the different types of bisalbuminemia of the laboratory of the biochemistry of the Ibn Rochd hospital in Casablanca. And to compare the results obtained with those of the literature, for new observations in terms of this subject, and formulating certain originalities which could be necessary for more advanced research on bisalbuminic cases.

Case Presentation

6 cases of bisalbuminemia were collected of 2083 serum protein electrophoresis carried out in the biochemistry laboratory of CHU Ibn Rochd of Casablanca of the year 2018.

Case No 1

A 27-year-old girl. She was hospitalized for an impure nephrotic syndrome objectifying to the puncture renal biopsy (PBR) of segmental and focal hyalinosis lesions. The patient was put on full-dose corticosteroid therapy. The biological assessment revealed a nephrotic syndrome characterized by hypoalbuminemia at 16g/l, hypoprotidemia at 45g/l and proteinuria at 6.7g/l.

Serum protein electrophoresis (Figure 1) is performed on the Capillarys® from the company Sébia identified a hypoalbuminemia (39.1g/l), hypogammaglobulinemia (6.6g/l), a significant increase in alpha-2 globulin (33.4g/l), a decrease in alpha-1 globulin to 1.1 g/l, a decrease in beta 1, a slight increase in beta 2. The total protein (43g/l) and the albumin/globulin ratio (0.64g/l). Profile electrophoresis has objectified a bisalbuminemia apart from pancreatitis and any treatment with betalactamine, this alloalbuminemia is characterized by a peak drop in the albumin fraction. And identifies a variant more rapidly migrating ahead of albumin at a lower rate than normal albumin.

Case No 1

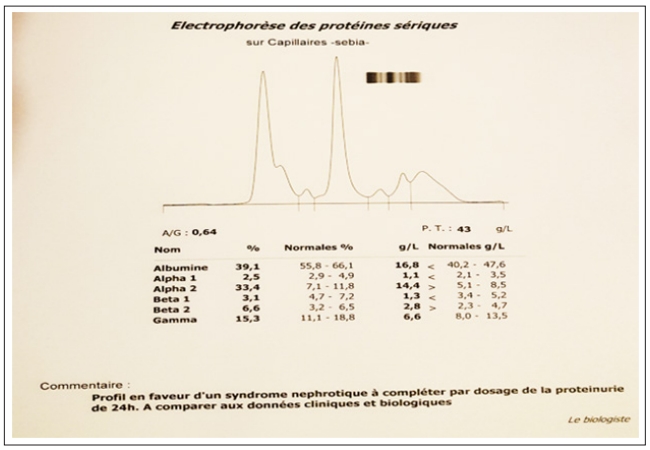

Figure 1: Electrophoretic Profile Case no 1

Case No 2

37-year-old female subject, with no particular medical history, she was admitted for tolerated anemia, clinical examination shows generalized mucocutaneous pallor, hemoglobin at 3g/l and she has diarrhea fluid accompanied by rectorrhagia of moderate size, all evolving in a febrile context. She also presents with chronic arthralgia with an inflammatory appearance.

Serum protein electrophoresis (Figure 2), objectified a bis albuminemia characterized by a slower variant with a level lower than normal albumin. Significant hypoalbuminemia (11.6 g/l), associated with a syndrome moderate inflammation. An increase in alpha-1 (8.8 g/l) and alpha-2 (11.5 g/l) and hypoprotidemia (46 g/l).

Case No 2

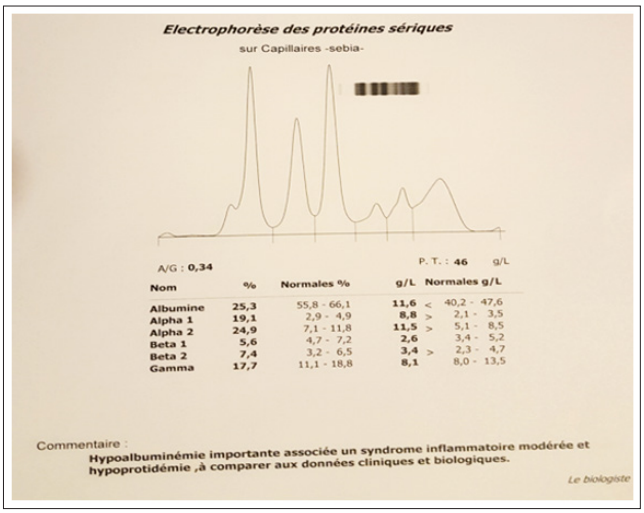

Figure 2: Electrophoretic Profile Case no 2

A transient and acquired bisalbuminemia has been identified after taking the antibiotic. And she started to fade away 8 days after stopping the antibiotic (Figure 3).

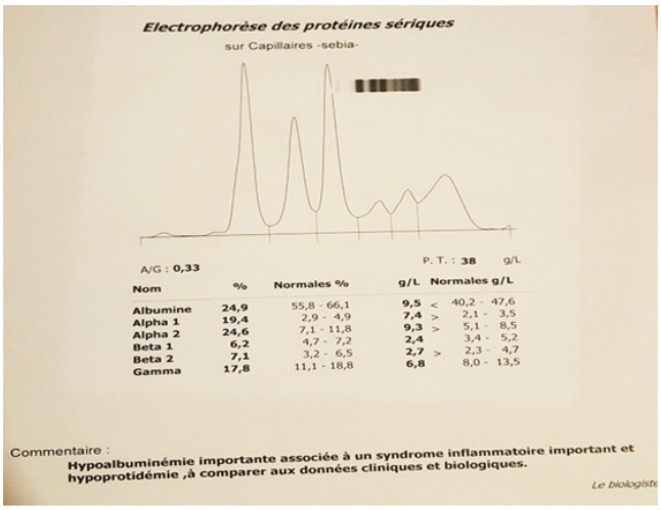

Figure 3: Electrophoretic Profile of Case Number 2 after Discontinuation of Beta-Lactams

Case No 3

45-year-old male subject. The biological assessment confirmed a nephrotic syndrome.

Capillary electrophoresis of serum proteins (Figure 4) revealed hypoalbuminemia (23.0 g/l), increase in alpha-2 (9.6 g/l), and hypogammaglobulinemia (3.8 g/l). The total protein (45g/l) and the albumin/globulin (1.4g/l). In addition, the electrophoretic profile identified bisalbuminemia apart from antibiotic treatment, and pancreatitis. Bisalbuminemia is characterized by duplication in fraction of albumin with the existence of a variant faster migrating forward than normal albumin with a rate lower than the normal peak.

Case No 3

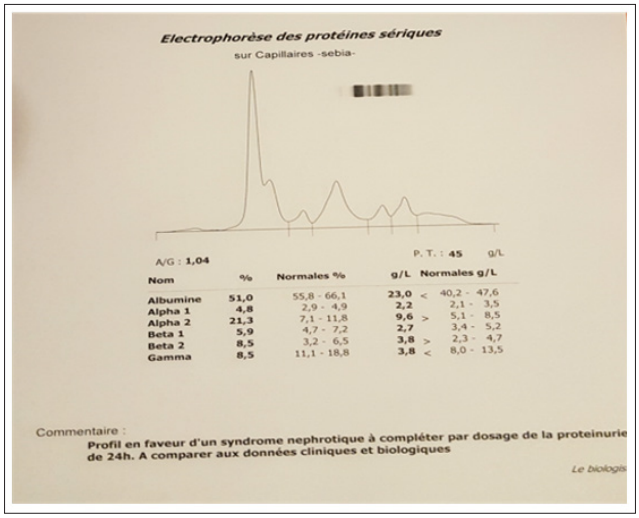

Figure 4: Electrophoretic Profile of Case Number 3

Case No 4

40-year-old male subject, with no particular medical history. The biological assessment confirmed a syndrome pure nephrotic without arterial hypertension, and an absence of hematuria and without renal insufficiency. Serum protein electrophoresis (Figure 5) identified hypoalbuminemia (25.5g/l), a decrease in alpha-1 (1.3g/l), a increase in alpha-2 (13.6 g/l) and hypogammaglobulinemia (2.7 g/l).

Case No 4

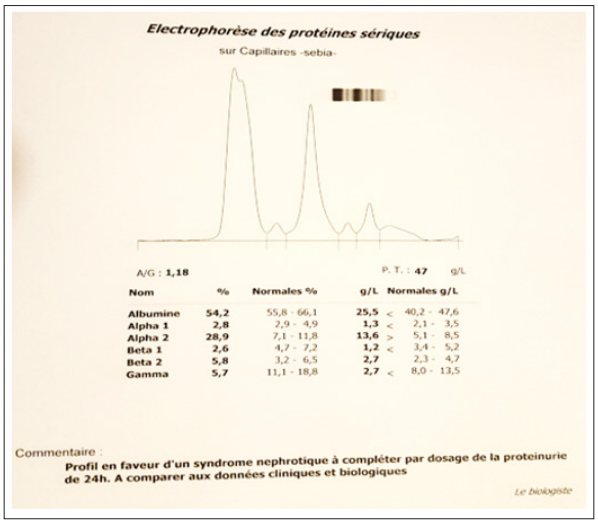

Figure 5: Electrophoretic Profile of Case Number 4

A proteinuria of 47 g/l, the albumin/globulin (1.18g/l). Again, the electrophoretic aspect objectified a bisalbuminemia apart from any treatment of beta-lactam and pancreatitis.

The patient is on "Lasix" diuretic treatment.

Case No 5

A 13-year-old girl has psoriatic arthritis. Serum protein electrophoresis of this patient (Figure 6), suggested a chronic inflammatory syndrome and revealed a proteinemia of 74 g/l, a albumin/globulin ratio (0.48 g/l). Significant hypoalbuminemia (24.1 g/l), a significant increase in alpha-1 (8.3 g/l), a significant increase in alpha-2 (17.5 g/l), and an increase in beta-2 and an increase polyclonal gamma globulin (15.4%).

Case No 5

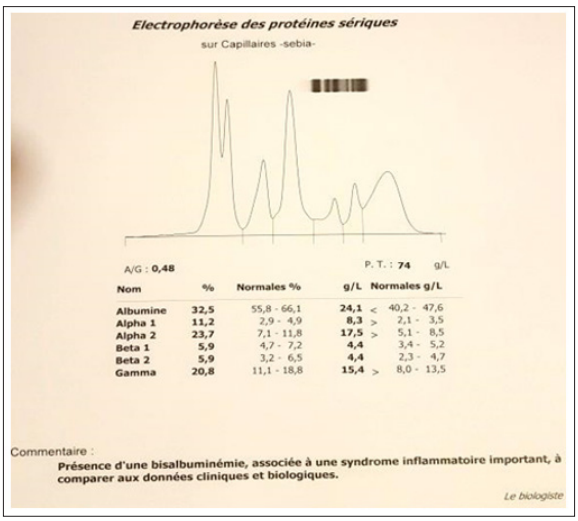

Figure 6: Electrophoretic Profile of Case Number 5

Acquired bisalbuminemia was observed, because the patient is on antibiotic treatment, particular beta-lactams.

Case No 6

40 years old male subject, who has had deep vein thrombosis for a year. Biological assessment showed a nephrotic syndrome with hypoalbuminemia (9.7 g/l), hypoprotidemia (32 g/l), hyperleukocytosis (28,000) per mm3 and the level of urea and creatinine is normal. Serum protein electrophoresis (Figure 7), objectified a hypo albuminemia (11.3 g/l) and increase in alpha-2 (12.5 g/l).

Case No 6

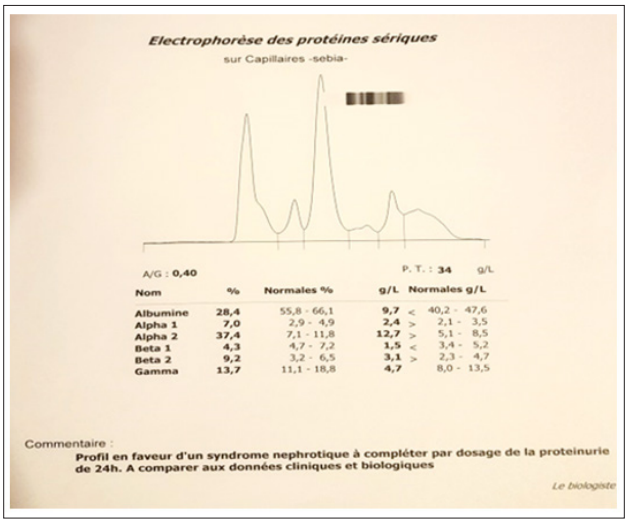

Figure 7: Electrophoretic Profile of Case Number 6

The patient is on treatment 3rd generation cephalosporins (C3G) 2g/d and Amoxicillin clavulanic acid 3g/d.

Transient and acquired bisalbuminemia began to appear after taking the antibiotic and accentuated after the taking another antibiotic in parallel with the first, which is shown in the second serum protein electrophoresis performed for the same patient (Figure 8).

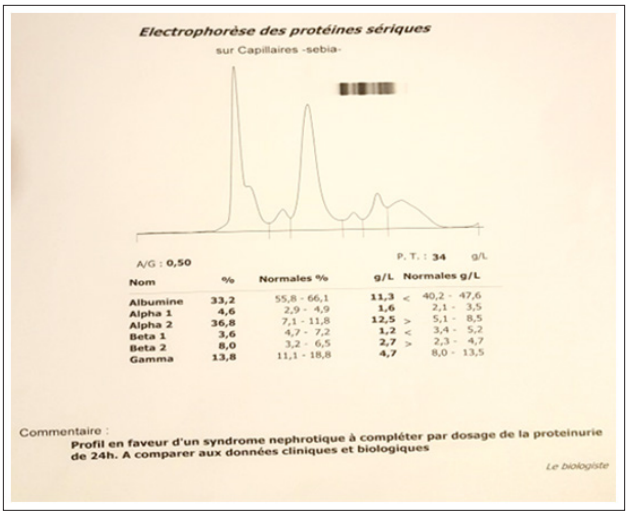

Figure 8: Electrophoretic Profile of Case Number 6 after Taking another Antibiotic

Discussion and Conclusions

The Three Cases of Bisalbuminemia Related to a Nephrotic Syndrome (Patients 1, 3 and 4)

The nephrotic syndrome is characterized by proteinuria at 3 g/day, hypoalbuminemia below 30 g/l, and hypoprotidemia less than 60 g/l. And it can be pure without kidney failure, high blood pressure and hematuria, or impure with the existence of these signs or certain [29]. Indeed, several authors have reported in the literature the presence of bisalbuminemia in the case of the syndrome nephrotic [23,30]. Therefore, until now we do not know the associated pathophysiological mechanism between the bisalbuminemia and nephrotic syndrome. As an exception, during nephrotic syndrome, albumin oxidizes extensively, which makes him more fragile [31]. A hypothesis to be accepted in these three cases.

The Three Cases of Bisalbuminemia Linked to Beta-Lactamin (Patients 2, 5 and 6)

The bisalbuminemia in these three cases is transient and acquired type due to the taking of the antibiotic, particular beta-lactams.

In both cases (5 and 6). This is a fast variant unlike case 2 where the variant is slower. In the literature, the association of bisalbuminemia and beta-lactam antibiotic treatment has already been elucidated [32]. The physiological mechanism is explained by the fixing of the antibiotic on a part of the albumin generating the bond between the carbamyl group and the lysine amino group of albumin [33]. Giving on an electrophoresis, a second peak of the bisalbumin in the albumin fraction. This peak becomes more marked if the dose of the antibiotic is increased [34]. That is confirmed in case 6, where the electrophoretic peak of the albumin variant fraction became more pointed when increased the dose of beta-lactam antibiotic.

Indeed, the peak is visible after three days to eight days of the administration of the antibiotic and it disappears after interrupt treatment for a few days to a few weeks. Case n°2, the bisalbumin peak has disappeared completely after a few days of stopping the antibiotic.

All the cases of bisalbuminemia collected in our work are of the transient and acquired type, three are linked to the syndrome nephrotic, and the other three are related to antibiotic treatment, particularly beta-lactams.

Indeed, the causal link of the bisalbuminemias has already been clarified in certain literatures.

Several cases have been reported by some authors concerning bisalbuminémie, in association with some diseases namely chronic kidney disease, sarcoidosis, type II diabetes, IgA myeloma…. Or is not sure if these bisalbuminemias are related to these pathologies or not [35-38]. Our wish is to report more cases and to clarify the pathophysiological mechanism involved. Bisalbuminemia is unknown in our center hospital. We want medical and paramedical staff to be informed about bisalbuminemia and encourage them to further research into this anomaly.

Availability of Data and Materials

All relevant data are present in the case report.

Acknowledgements

This study was supported by the laboratory of chemistry-biochemistry, environment, nutrition, and health, faculty of medicine and pharmacy, Hassan II University, Casablanca, and biochemistry laboratory, CHU Ibn Rochd of Casablanca, Morocco.

Funding
This work has not received any external funding.

Ethics Declarations
Ethical Approval and Consent to Participate
The study was approved by the Institutional Review Board of the Faculty of Medicine, and Pharmacy, Hassan II University, Casablanca. (Registration no.26/18). The study was conducted within the Biochemistry Laboratory, CHU Ibn Rochd of Casablanca, Morocco. The patient provided written informed consent to participate.

Consent for Publication
The patient provided written informed consent for publication.

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