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A Case of Bisalbuminemia Associated with Nonsteroidal Anti-Inflammatory Drug-Induced Nephrotic Syndrome

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Summary

Bisalbuminemia is a rather rare protein anomaly characterized by the presence of two distinct fractions of albumin on Serum Electrophoresis (SEP). It reflects the presence, in the same individual, of a normal albumin and a modified albumin.

The hereditary form is permanent whereas the acquired bisalbuminemia is transient and usually observed during treatment with beta-lactams, acute pancreatitis, rupture of pancreatic pseudocysts and monoclonal gammopathies. We report the case of a 49-year-old female, who was recently diagnosed with ankylosing spondylitis, is admitted to the service of Internal Medicine at the Moulay Ismaïl Military Hospital of Meknes after having presented anasarca, oliguria and nausea following treatment with anti-Inflammatory drugs (NSAIDs) for diffuse polyarthritis. Biological assessment showed nephrotic syndrome (ND) without renal insufficiency, and the electrophoresis performed on Capillarys® (Sebia) revealed a bisalbuminemia. Moreover, the renal biopsy showed a Glomerular Tip Lesion (GTL).

Through this work, we wish to report an unusual case of bisalbuminemia in order to familiarize clinicians, laboratory personnel and scientists with this protein anomaly, to discuss some of its physiopathological and practical aspects and to draw attention to a little known renal complication of NSAIDs (GTL associated with NS).

Keywords: Nonsteroidal anti-inflammatory drugs; Bisalbuminemia; Electrophoresis; Nephrotic syndrome

Introduction

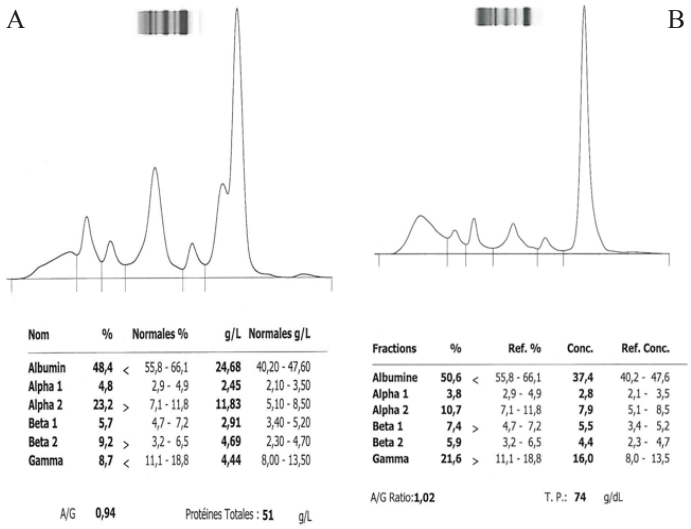
Bisalbuminemia is a rarely encoutered electrophoretic anomaly of albumin characterized by a bifid albumin peak on the serum protein electrophoresis. It reflects the presence, in the same individual, of normal plasma albumin and modified albumin. Depending on the electrophoretic mobility of the variant, bisalbuminaemia is said to be “rapid” in the case of migration faster than normal albumin or “Slow” otherwise. Bisalbuminemia can be inherited or acquired. The hereditary form is autosomal dominantly inherited and occurs with a cumulative frequency varying from 0.7 per 1000 to 1/8500 depending on the studied populations. The prevalence of acquired forms of bisalbuminemia is unknown, but these disorders have been reported in several pathological situations (Table 1). In this article, we report the case of a patient followed for ankylosing spondylitis, who presented with bisalbuminemia under unusual circumstances, nephrotic syndrome induced by non-steroidal anti-inflammatory drugs (NSAIDs) [1-4].

Table 1: Pathological situations associated with acquired bisalbuminemia.

1. Treatment with high doses of beta-lactams: Cephalosporins. Penicillins.
2. Pancreatitis: Rupture of pancreatic pseudocysts. Pancreatic fistulas.
3. Monoclonal gammopathies: Multiple myeloma. Benign monoclonal immunoglobulin.
4. Hepatopathies: Autoimmune hepatitis. Hepatic cirrhosis. Adenocarcinoma liver metastases.
5. Hyperamylasemia.
6. Hypothyroidism and diabetes.
7. Alzheimer disease.
8. Chronic renal failure. Nephrotic syndrome with minimal glomerular lesions.

Observation

Electrophoresis of the serum proteins of a 49-year-old woman, carried out by capillary electrophoresis on Capillarys® (Sebia) reveals a proteinemia at 51 g / L (64-83 g / L) and a bifid peak of the albumin (Figure 1). The patient, recently diagnosed with ankylosing spondylitis, was admitted to the Internal Medicine department of Moulay Ismaïl Military Hospital in Meknes after having presented hydrops, oliguria and nausea following treatment with NSAIDs for diffuse polyarthralgia. Interrogation reveals no history of liver disease, neoplasia and no antibiotics intake, especially beta-lactams.



A) Electrophoretic profile of the patient on admission showing bisalbuminemia associated with nephrotic syndrome. Bisalbuminemia was not detected on the agarose gel; **B)** Absence of bisalbuminemia 3 months previously.

Figure 1: Serum protein electrophoresis on Capillarys II.

A laboratory examination revealed a nephrotic syndrome with massive 24-hour proteinuria at 922 mg / L [20-140], hypoalbuminemia at 22 g / l [34-45], hyperlipidemia at 3.45 g / l without renal failure or hematuria (Table 1). Moreover, the amylasemia was 26 IU / L [22-51 IU / L], indicating the absence of pancreatitis. The ionogram, hepatic and inflammatory tests, as well as the C 3 and C4 fractions of the complement were normal (Table 2).

Table 2 : Results of the patient's biological assessment.

Laboratory examinations	Parameters	Results
Renal assessment	Urea (0.21-0.43 g/l)	0.28
	Creatinine (5-12 mg/l)	6
	Uric acid (23-61 mg/l)	30
	Albumine (34-45 g/l)	22
	24H Proteinuria (20-140 mg/l)	922
Liver function	ASAT (5-35 UI/L)	14
	ALAT (5-35 UI/L)	11
	GGT (5-39 UI/L)	16
	PAL (35-104 UI/L)	71
	Total bilirubin (0-10 mg/l)	3
Lipid profile	Total cholesterol (1.35-2.07 g/l)	3.45
	HDL Cholesterol (0.45-0.75 g/l)	0.51
	LDL Cholesterol (0.6-1.4 g/l)	2.8
	Triglycerides (0.22-1.6 g/l)	0.69
Markers of inflammation	C-Reactive Protein (0-4.5 mg/l)	43.55
	Erythrocyte Sedimentation Rate (<20 mm/h)	25
	Ferritin (20-300 µg/L)	123
	Complement fraction C3c (0.9-1.8 g/l)	1.59
	Complement fraction C4 (0.1-0.4 g/l)	0.34
Electrolytes	Sodium (135-145 mmol/l)	141
	Potassium (3.5-5.11 mmol/l)	3.98
	Chlorure (95-105 mmol/l)	101
	Calcium (85-100 mg/l)	90.4

The suspected drug, meloxicam, was stopped and anti-proteinuric treatment with corticosteroids and diuretics was started. The evolution was marked by complete clinical and biological remission with resolution of edema and regression of proteinuria, hypoprotidemia and hyperlipidemia. However, further investigation could not be performed as the patient was discharged from the hospital and lost to follow-up.

Since a previous SEP, performed three months before, on account of inflammatory polyarthralgia, was normal (Figure 1), the permanent and therefore hereditary nature of bisalbuminemia was excluded. In addition, the renal biopsy showed a glomerular nephropathy of Glomerular Tip Lesion (GTL) type. Thus, the diagnosis of bisalbuminemia associated with a NS induced by NSAIDs was retained.

Discussion

Described for the first time in 1955 by Scheurlen, bisalbuminemia is a rarely encountered dysproteinemia characterized by the coexistence in the same individual of two types of serum albumin of different electrophoretic mobility, normal albumin and a variant thereof called "fast" or "slow" type depending on whether it migrates more or less quickly than normal albumin.

Its detection has now become more frequent in biological laboratories, having routinely replaced the classic technique of electrophoresis on agarose gel by capillary electrophoresis, a more sensitive technique allowing better resolution of protein fractions [1-4]. In fact, in the reported clinical case, it is observed that the modified albumin was only revealed by capillary electrophoresis on Capillarys II (Sebia), showing a gain in the separation performance of this technique compared to the agarose gel. As many clinical biology laboratories have routinely replaced the classic technique of agarose gel electrophoresis by capillary electrophoresis, the frequency of detection of bisalbuminemia is likely to increase in parallel with the use of capillary electrophoresis [4,5].

Furthermore, the difference in electrical mobility observed in our patient between the two types of albumin was in favor of a difference in chemical composition and/or molecular weight [1,2]. However, neither the difference in amino acid composition nor the difference in renal excretion of the two proteins could be studied because on the one hand the patient was lost to follow-up, and on the other hand due to the limitations of our laboratory techniques.

This electrophoretic abnormality can be inherited or acquired. The hereditary form is permanent and reflects the coexistence of two types of albumin. It is caused by an autosomal dominant monofactorial mutation in the albumin gene. Currently, more than 100 albumin variants have been identified [1,2]. Although no adverse effects are attributed to this, some albumin variants may have a different affinity than normal albumin towards steroid and thyroid hormones, metal ions, fatty acids, or drugs, which increases their general concentration in blood.

Therefore, the recognition of albumin variants by laboratory personnel may provide information on the pathophysiology of diseases related to this anormal binding of these ligands to albumin [2,4,6,7]. Additionally, bisalbuminemia is an interesting laboratory incident whose importance lies in helping identify sites of action for certain drugs [1].

The presence of a history of normal electrophoretic tracing in our patient made it possible to exclude the permanent hereditary nature of bisalbuminemia in order to retain the acquired character. This is usually transient and results from structural changes in some of the circulating albumin either by subtraction or by addition of material. It usually has no pathological significance, except for that associated with a pseudocyst of the pancreas. The existence of bisalbuminemia, whatever its etiology, does not, however, lead to either hyperprotidemia or hyperalbuminemia [2,3].

In fact, acquired bisalbuminaemia can appear after rupture of a pancreatic cyst in a serous cavity, releasing pancreatic enzymes which will digest part of the albumin. A modified albumin results from the partial proteolysis of native albumin by chymotrypsin and carboxypeptidase. The digested and undigested albumin fractions migrate differently on electrophoresis where they make two distinct peaks. Bisalbuminemia can also occur by binding of monoclonal immunoglobulin to albumin in subjects with myeloma, giving it slower electrophoretic properties in agarose. Ig that can easily be complexed with albumin are most often IgA, more rarely IgM. Finally, transient bisalbuminaemia can also result from treatment with a high dose of beta-lactam antibiotics.

The appearance of two peaks is explained by the binding of antibiotics to a part of the albumin, the opening of the beta-lactam ring is followed by the bond between the carbamyl group of this ring and the amino group of a lysine of the albumin. The modified albumin migrates differently from normal albumin resulting in a second peak on electrophoresis, all the more marked as the dose of antibiotic administered is high or as its elimination is delayed by renal failure [2-4,8].

None of these aetiologies can be retained in the case presented in the absence of a history of treatment with beta-lactams, pancreatic anomaly and monoclonal immunoglobulin. The physiopathological mechanism in the reported case remains unexplained, as is moreover the case of acquired bisalbuminemia associated with other pathological contexts (chronic renal diseases, hepatic adenocarcinoma metastases, Alzheimer's disease, sarcoidosis, hypothyroidism) [1,3,9,10].

Moreover, in our patient, we noticed that the albumin variant migrated less quickly than normal albumin, suggesting that its size is larger or that its load is less pronounced than normal albumin [4,5]. It would therefore be possible that this variant is the result of a more lasting binding to the autoantibodies present in our patient followed for autoimmune disease. However, more studies are needed to better understand the etiology and the physiopathological and clinical significance of this albumin variant [11].

Variations in albumin, whether inherited or acquired, should attract the attention of biologists, clinicians and researchers. Some forms can give information about protein evolution, molecular structure and characteristics of the albumin molecule. The acquired form can guide the clinician to an underlying etiology such as pseudocysts of the pancreas, while the study of albumin variants can help in the estimation of the geographical distribution of these variants, which is interesting from an anthropological point of view [11].

Conclusion

Through this work, we wish to report the unusual case of a bisalbuminemia associated with a GTL associated with NS closely related to the use of NSAIDs in order to familiarize clinicians, laboratory staff and scientists with this protein anomaly, to discuss certain physiopathological and practical aspects and to draw attention to a little-known renal complication of MLX (GTL associated with NS induced by NSAIDs).

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