Metabolism Open 23 (2024) 100307

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.sciencedirect.com/journal/metabolism-open

Incidental detection of hereditary bisalbuminemia in a patient with positive DAT coombs: A case-based review

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ARTICLE INFO

Keywords:
Albumin
Bisalbuminemia
Bisalbuminuria
Congenital analbuminemia
Familial dysalbuminemic hyperthyroxinemia
Hypertriiodothyroninemia
Serum protein electrophoresis

ABSTRACT

Bisalbuminemia is a rare, typically benign condition marked by the presence of a bifid albumin band on serum protein electrophoresis. It can either be inherited due to a point mutation or acquired in association with various medical conditions, most commonly diabetes mellitus. Bisalbuminuria, the presence of bifid albumin in urine, may or may not accompany bisalbuminemia. Both conditions are often discovered incidentally during screening for monoclonal gammopathy. Bisalbuminemia and related variants provide insights into albumin's genetic diversity and functional roles, influencing clinical diagnostics and research in human genetics. Understanding these variants aids in distinguishing benign conditions from potential disease states, guiding appropriate clinical management. In this case-based review, we present a case of hereditary bisalbuminemia identified unexpectedly during an investigation of a positive Direct Antiglobulin Test Coombs in an adult female patient. This review aims to highlight the key features of bisalbuminemia, a rare condition that should be recognized by clinicians.

1. Introduction

Human serum albumin (ALB) is a vital component of human plasma, constituting 60–65 % of total plasma proteins. This protein plays a crucial role in maintaining the oncotic pressure of the plasma. Additionally, albumin is instrumental in the transport of various molecules, antioxidation, anticoagulation, and human immunity.

Serum Protein Electrophoresis (SPE) and Urine Protein Electrophoresis (UPE) are commonly utilized screening tests for monoclonal gammopathies [1]. Typically, the electrophoresis pattern reveals albumin as the largest discrete peak, followed by the five globulin fractions: alpha1, alpha2, beta1, beta2, and gamma [2]. Occasionally, two peaks are observed in the albumin region, either completely distinct or partially split. This phenomenon is termed bisalbuminemia or alloalbuminemia when detected in serum plasma, or bisalbuminuria when identified in a urine sample. Bisalbuminemia can be hereditary, resulting from a point mutation, or acquired, associated with various medical conditions [3,4].

In this case-based review, we present a case of a 66-year-old female whose SPE revealed a bifid albumin band. We also review the limited literature on this rare condition. Our aim is to raise awareness of bisalbuminemia and familiarize clinicians with this unusual electrophoresis pattern.

2. Case presentation

A 66-year-old female patient presented to our clinic with a previously detected positive Direct Antiglobulin Test (DAT Coombs) for further investigation. Her past medical history was unremarkable, except for the presence of uterine leiomyomas. She reported no recent drug intake. Clinical examination revealed no significant findings. Initially, we investigated the cause of the positive DAT Coombs test (IgG++). Hemolytic anemia and other potential causes were excluded. We hypothesized that the positive test could be attributed to the

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https://doi.org/10.1016/j.metop.2024.100307
Received 22 July 2024; Received in revised form 27 July 2024; Accepted 29 July 2024
Available online 30 July 2024

Abbreviations:

AFP	Alpha-fetoprotein
AGE	Agarose Gel Electrophoresis
ALB	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CAA	Congenital Analbuminemia
CEA	Carcinoembryonic Antigen
CKD	Chronic Kidney Disease
CPK	Creatine Phosphokinase
CZE	Capillary Zone Electrophoresis
DAT	Direct Antiglobulin Test
ESR	Erythrocyte Sedimentation Rate
FDH-T3	Familial Dysalbuminemic Hyperthyroxinaemia (related to T3)
FDH-T4	Familial Dysalbuminemic Hypertriiodothyroninaemia (related to T4)
fT3	free Triiodothyronine
fT4	free Thyroxine
γ-GT	Gamma Glutamyltransferase
Hb	Hemoglobin
HbA1c	Glycated Hemoglobin A1
Ht	Hematocrit
LDH	Lactate Dehydrogenase
PLT	Platelets
SIFE	Serum Immunofixation Electrophoresis
SPE	Serum Protein Electrophoresis
TBIL	Total Bilirubin
TG	Thyroglobulin
TSH	Thyroid Stimulating Hormone
UPE	Urine Protein Electrophoresis
WBC	White Blood Count

patient's history of multiple blood transfusions due to polymenorrhea related to the uterine leiomyomas. Additional laboratory studies, including serum glucose and thyroid hormone levels, were within normal limits.

SPE revealed a bifid albumin band. The patient's serum total protein concentration was 7.53 g/dL, with albumin at 4.25 g/dL and globulins at 3.28 g/dL, resulting in an albumin-globulin ratio of 1.3. The persistence of two distinct albumin bands in repeated SPEs performed at different chronic periods strongly suggested the diagnosis of bisalbuminemia. We meticulously assessed conditions associated with acquired bisalbuminemia. In particular, malignancy was excluded as tumor markers (CEA, CA-19-9, CA-15-3, CA-125, and AFP) were within normal ranges, and imaging via computed tomography of the chest and abdomen, along with upper and lower gastrointestinal endoscopies, revealed no pathological findings. Mammography did not show any abnormal findings. Furthermore, bone marrow aspiration and screening for paraproteinemia were normal. Finally, multiple auto-antibody testing was negative, including rheumatoid factor, antinuclear antibodies, anti-DNA antibodies and antibodies against Extractable Nuclear Antigen while C3 and C4 were within normal range.

Based on these findings, the scenario of genetic bisalbuminemia was strongly suggested. We recommended genetic testing to confirm hereditary bisalbuminemia, but the patient declined due to financial constraints. Consequently, the diagnosis remains supported as an exclusion diagnosis. Table 1 presents blood laboratory findings of the patient.

The SPE results are depicted in Fig. 1A and B. The patient provided informed consent for the publication of her case and laboratory findings.

3. Discussion

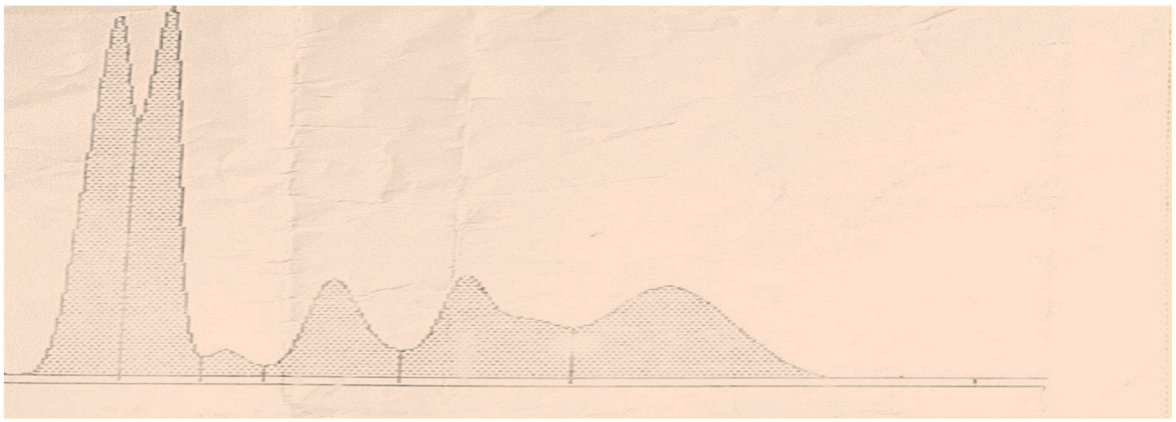
Human serum ALB is the predominant protein in plasma, comprising 60–65 % of total proteins. Synthesized by hepatocytes at a rate of 14 g per day in healthy adults, ALB plays essential roles in maintaining oncotic plasma pressure, contributing approximately 80 % of this pressure. It is also renowned for its ability to bind less soluble and hydrophobic ligands, serving as a crucial transporter for various endogenous and exogenous molecules. ALB functions as an antioxidant and plays roles in immunity and anticoagulation by binding to antithrombin and inhibiting platelet aggregation [5–7].

Structurally, ALB is a 66.5 kDa single polypeptide chain of 585 amino acids, predominantly composed of α-helices (67 %) without β-sheets. It forms a heart-shaped molecule with three homologous domains, each consisting of two subdomains (A and B). ALB has a net charge of −15 at physiological pH, preventing it from permeating capillary walls. The

Table 1
Main blood laboratory findings in our patient.

Blood Laboratory parameters	Normal range	Patient's value
WBC	4.000–10.000/mm^3	8.100
Hb	14–18 g/dl	13.6
Ht	38–52 %	42.4
PLT	140.000–450.000/mm^3	323.000
ESR	0–20 mm/h	18
Glucose	70–105 mg/dL	98
HbA1c	<6.5	5.7
Urea	15–38 mg/dL	28
Creatinine	0.7–1.3 mg/dL	0.9
Sodium	135–145 mmol/L	145
Potassium	3.5–5.5 mmol/L	4.5
SGOT	15–48 U/L	18
SGPT	13–40 U/L	20
ALP	53–128 U/L	69
γ-GT	9–50 U/L	16
Total proteins	6–8.3 g/dL	7.53
Albumin	3.4–5.4 g/dL	4.25
Globulins	2.0–3.5 g/dL	3.28
LDH	230–460 mg/dL	278
TBIL	0.2–1.2 mg/dL	0.43
Amylase	27–102 U/L	52
CPK	24–170 U/L	72
Triglycerides	40–160 mg/dL	137
Total cholesterol	140–220 mg/dL	193
Uric acid	2.6–6 mg/dL	3.9
TSH	0.5–5.0 mIU/L	2.02
fT3	3.1–6.8 pmol/L	2.84
fT4	0.8–1.9 ng/dL	1.17
B12	223–1132 pg/mL	260
Folic acid	3.1–12.4 ng/mL	6,9
Ferritin	14–186 ng/mL	23
Haptoglobin	0.5–2.2 g/L	2.02
Cold agglutinins test	Negative	Negative
CEA	0–10 ng/mL	0.6
CA-19-9	0–37 U/mL	8.9
CA-15-3	0–30 U/mL	14.5
CA-125	0–35 U/mL	6.4
AFP	0–37 ng/mL	2.1

Abbreviations: AFP: Alpha-fetoprotein; ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CEA: Carcinoembryonic Antigen; CPK: Creatine Phosphokinase; ESR: Erythrocyte Sedimentation Rate; fT3: free Triiodothyronine; fT4: free Thyroxine; γ-GT: Gamma Glutamyltransferase; Hb: Hemoglobin; HbA1c: Glycated Hemoglobin A1; Ht: Hematocrit; LDH: Lactate Dehydrogenase; PLT: Platelets; TBIL: Total Bilirubin; TG: Thyroglobulin; TSH: Thyroid Stimulating Hormone; WBC: White Blood Count.



Fractions	%	% Normal
Albumin 1	25.6	54.2-67.0
Albumin 2	35.7	2.4-4.6
Alpha 1	1.9	2.0-5.0
Alpha 2	10.6	6.5-13.5
Beta	15.7	9.1-14.7
Gamma	20.5	10.0-18.6

Fig. 1A. The results of serum protein electrophoresis in our patient. Presence of two albumin components (bands) at the left side.

Fig. 1B. Electrophoretic pattern with a bifid albumin band at the left side.

ALB gene spans 16,961 nucleotides on chromosome 4, comprising 15 exons symmetrically placed within the protein's domains. Expressed in a co-dominant manner, both alleles contribute equally to ALB production [8].

Genetically, ALB exhibits significant polymorphism, resulting in various isoforms, such as bisalbuminemia, characterized by the presence of two distinct ALB molecules. Bisalbuminemia was first described in 1955 by Scheurlen in a patient with diabetes mellitus and can be classified as either hereditary or acquired. The incidence of bisalbuminemia varies widely depending on race, nationality, and region. High occurrence rates are noted in small, isolated populations, such as indigenous North American Indians, where the incidence is approximately 1 in 100. Conversely, in European populations, heterozygosity ranges from 1 in 1000 to 1 in 10,000 [2,3,9–11]. To the best of our knowledge, in Greece, only three published cases of bisalbuminemia have been reported so far [9,12,13]. Accordingly, recent evidence reports low incidence rates of inherited bisalbuminemia in Southern China, with an average incidence estimated at 0.0264 % [14].

Hereditary bisalbuminemia, typically asymptomatic, results from autosomal co-dominant inheritance of point mutations in the ALB gene, with approximately 65 different mutations identified to date [9,15]. On the contrary, the acquired form of bisalbuminemia, which may be transient, has been associated with various conditions. Diabetes mellitus is suggested as the most common cause, although the underlying mechanism is not yet clear. Regarding pancreatic pseudocysts, protein lysis by pancreatic enzymes is likely responsible for the double peak observed during electrophoresis [16]. On the other hand, beta-lactam antibiotics can bind to albumin and alter its electrophoretic migration pattern [3]. Moreover, isolated cases of the coexistence of bisalbuminemia with allergic bronchopulmonary aspergillosis and various categories of solid organ malignancies, including cholangiocarcinoma, digestive adenocarcinoma, and metastatic lung carcinoma, have been described [17–20]. The main causes of bisalbuminemia are illustrated in Fig. 2 [21–23].

Both hereditary and acquired forms are often incidentally discovered during screenings for monoclonal gammopathy. However, there is no known association or pathophysiological relationship between bisalbuminemia and monoclonal gammopathy. In fact, the recognition of bisalbuminemia in these cases is likely due to the routine performance of SPE and UPE in this population, with the incidence in these subjects expected to be similar to that of the general population [24].

For laboratory detection of bisalbuminemia, SPE or serum immunofixation electrophoresis (SIFE) may reveal two distinct peaks or a partial splitting of the albumin peak. This phenomenon is caused by single amino acid substitutions that alter the electrophoretic migration of ALB [25]. However, agarose gel electrophoresis (AGE) has been shown to be ineffective in identifying bisalbuminemia. Consequently, capillary zone electrophoresis (CZE) is the preferred diagnostic method due to its superior discriminatory and resolution capabilities [9,26]. Additionally, advanced techniques such as electrospray mass spectrometry can identify additional variants with minimal charge differences (silent albumins), suggesting that the prevalence of bisalbuminemia may be underestimated [27].

Bisalbuminemia is differentiated from other conditions during SPE to ensure an accurate diagnosis. Bisalbuminemia should not be mistaken for an abnormal globulin peak, especially when electrophoresis is performed in the investigation of monoclonal gammopathies and when the additional band appears in the same region as albumin. The differential diagnosis of such an additional band includes various conditions, the most common being artifacts of electrophoresis due to air bubbles, gel distortions, and overloading. In these cases, repeating the electrophoresis will result in the disappearance of the additional band. Secondly, proteins that normally migrate in the same region as albumin may be elevated and mimic the appearance of bisalbuminemia. Such proteins include pre-albumin (which increases after recent food ingestion), alpha 1 acid glycoprotein (an acute phase reactant), and alpha lipoproteins. However, any unusual band on an SPE may indeed be a true paraprotein, and a monoclonal gammopathy should always be considered, especially since light chains can migrate to abnormal locations. Bands due to acute phase reactants and food ingestion are temporary and do not occur on

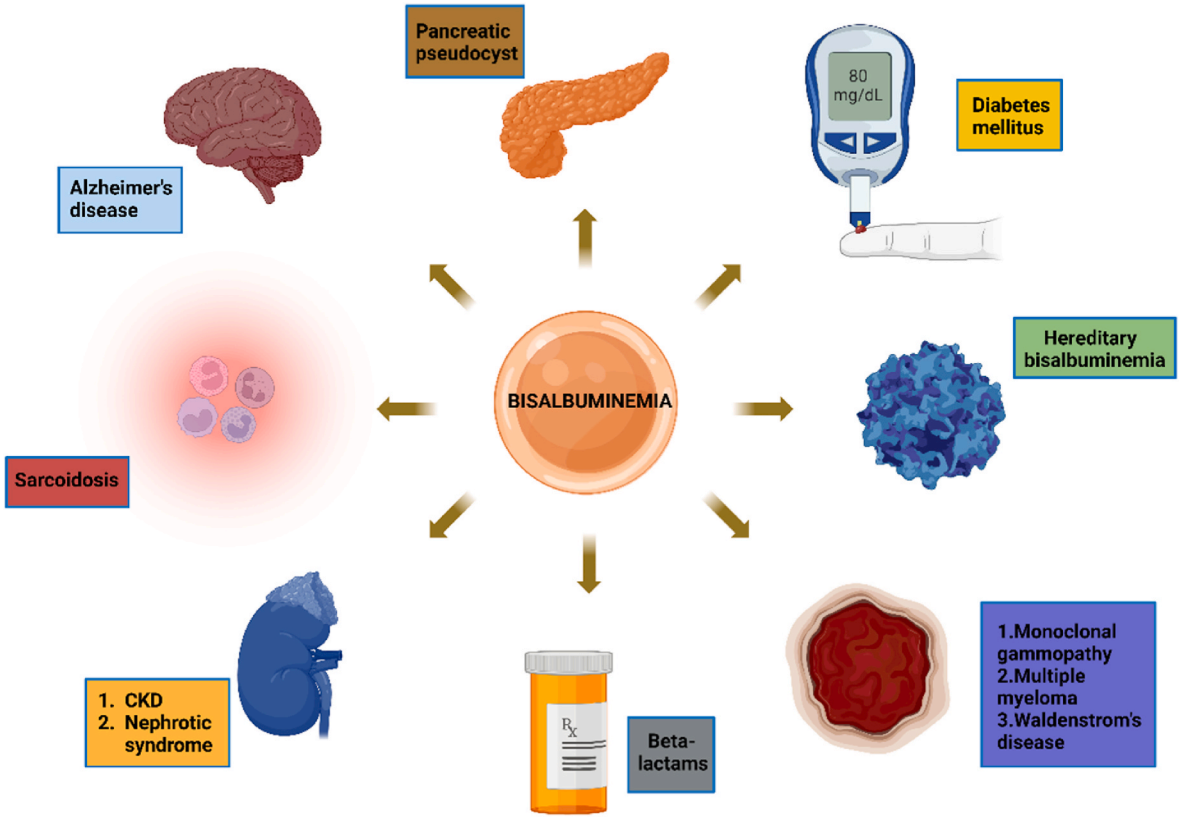


Fig. 2. Main causes of bisalbuminemia. Created with www.BioRender.com. (assessed on July 21, 2024).

SPE in repeated tests [27,28].

In bisalbuminemia, most albumin isoforms are functionally normal, and the majority of individuals exhibit normal serum albumin concentrations [2]. Typically, bisalbuminemia has no clinical significance and is of interest primarily for human genetics due to its rare incidence. However, distinguishing between the inherited and acquired forms is important when it is detected. The detection of bisalbuminemia secondary to an acquired ALB variant should raise suspicion and could assist clinicians in investigating an underlying disease that has not yet been diagnosed. The detection of alloalbumins may also serve as an innovative tool to track millennial human migration [3].

Moreover, genetic variants with known mutations can provide valuable molecular information about ALB binding sites, antioxidant and enzymatic properties, and stability. Notably, some albumin variants may have altered affinities for certain hormones, like thyroxine, metal ions, fatty acids, and drugs, decreased half-lives, or reduced thermal stability, which can have clinical relevance [29]. Certain ALB variants, such as those causing Familial Dysalbuminemic Hyperthyroxinemia (FDH-T3) or Hypertriiodothyroninemia (FDH-T4), affect hormone binding and pharmacokinetics [30–32].

Four specific mutations (218 Arg→His, 218 Arg→Pro, 218 Arg→Ser, and 222 Arg→Ile) have been associated with FDH-T3, and the 66 Leu→Pro mutation with FDH-T4. FDH-T3 and FDH-T4 are dominantly inherited syndromes characterized by elevated concentrations of thyroid hormones in the bloodstream. These syndromes do not cause disease because the concentration of free hormones remains normal. These variants of ALB are not detectable by electrophoresis, so protein and/or DNA sequencing of the ALB gene should be performed to avoid inappropriate surgical or drug treatment of euthyroid subjects. FDH-T4 is the most common cause of euthyroid hyperthyroxinemia in Caucasians. These mutations can also affect the binding of other ligands and potentially alter the pharmacokinetics of ALB-binding drugs [30–32].

On the other hand, Congenital Analbuminemia (CAA) is an autosomal recessive disorder characterized by the absence or a low level of ALB in serum due to variations in the ALB gene, and it has significant clinical implications. This very rare condition is found in approximately 1 in 1,000,000 individuals. In adults, CAA is generally benign because of compensatory increases in other plasma proteins, and affected adults typically present with mild edema, hypotension, and fatigue. A distinctive lower body lipodystrophy has also been described in these patients. In contrast, CAA is life-threatening during the prenatal and perinatal periods, often causing miscarriages and preterm births. It can also lead to death in early childhood due to fluid retention and pulmonary infections. To date, 28 different mutations have been identified in individuals with CAA. Most of these causative molecular defects have been detected in a single individual or in members of a single family [33,34].

4. Conclusions

Human serum albumin is a critical component of plasma, serving essential functions in maintaining oncotic pressure, transporting molecules, and contributing to various physiological processes such as antioxidation and immunity [1,35]. Bisalbuminemia, a rare condition characterized by the presence of two distinct albumin peaks on electrophoresis, can either be hereditary or acquired. While hereditary forms are typically benign, acquired bisalbuminemia may be associated with underlying medical conditions. This case-based review highlights the importance of recognizing unusual electrophoresis patterns to improve diagnostic accuracy and clinical management. Further research into albumin variants contributes to our understanding of genetic diversity and aids in distinguishing between benign variants and potential disease states, thereby guiding appropriate patient care strategies.

Funding

This research received no external funding.

Institutional review board statement

Not applicable.

Informed consent statement

The patient has provided informed consent to the publication of her case and laboratory results.

Data availability statement

Not applicable.

CRediT authorship contribution statement

Elena Avgoustou: Writing – original draft. **Dimitris Kounatidis:** Writing – review & editing. **Natalia G. Vallianou:** Writing – original draft. **Irene Karampela:** Writing – original draft. **Theodora Stratigou:** Writing – original draft. **Maria Dalamaga:** Writing – review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

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