

Clinical practice

Allergic bronchopulmonary aspergillosis coexists with hereditary bisalbuminemia

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The electrophoresis of a patient's serum proteins occasionally reveals two distinct fractions of serum albumin. This rare phenomenon is called bisalbuminemia. Bisalbuminemia can be classified into two types, a rare hereditary one and non-hereditary bisalbuminemia. There have been many reports about non-hereditary bisalbuminemia, which is mainly caused by the excess-use of antibiotics such as penicillin. Hereditary bisalbuminemia (or alloalbuminemia) is a rare, autosomal, and incomplete dominant hereditary condition characterized by the presence of two distinct fractions of serum albumin by electrophoresis. Scheurlen¹ reported the first case of this disease in 1955. The first case of hereditary bisalbuminemia in China was reported by Ying et al² in 1980. Since then, approximately 130 cases of bisalbuminemia from 21 different families have been reported in China. Here, we described a new family with hereditary bisalbuminemia, which was discovered with a patient complained of refractory asthma.

A 44-year-old man complained of recurrent wheeze for one and half years. He was ever diagnosed with asthma based on lung function test. After received standard asthma treatment prescription: inhaled steroid plus long active β_2 agonists (ICS+LABA), his symptoms were not alleviated yet. He had to often take some oral steroids and seems to be like hormone dependent asthma, one type of refractory asthma. The patient came to our hospital on July 28, 2012.

When admitted to our hospital, the patient had normal basic physiological index including body temperature, breathing rate, heart rate, blood pressure and arterial blood gas analysis. There were rough noises in both lungs and there were no extensive crackling noises. His lung functional test showed forced expiratory volume in one second (FEV₁) was 2.12 L/min (accounted for 58.8% of the expected value) and FEV₁/forced vital capacity (FVC) was 61.7%, which showed a positive result of bronchodilation test and *Aspergillus* antigen intradermal test. Total serum IgE level was 674 kU/L, and the specific IgE level for aspergillosis was negative. The proportion of eosinophile granulocyte in sputum was 86% and reduced to 5% after steroid treatment. Thorax CT examination revealed no bronchiectasis. According to the *Clinical Practice Guidelines of the Infectious Diseases Society of America*,³ this patient was finally diagnosed with allergic bronchopulmonary aspergillosis (ABPA). After treated with 50/500 μ g

salmeterol/fluticasone twice a day, 18 μ g of tiotropium once a day and 40 mg of prednisone once a day, there was a quick relief for his symptoms.

Routine laboratory examination showed that the total amount of serum proteins of this patient was 65 g/L, and the amount of albumin (ALB) was 41 g/L, which were within the normal range. Sebia automated capillary electrophoresis system (Sebia, French) was used to analyze the serum proteins of this patient. The capillary electrophoresis profile revealed two peaks (Figure 1A). The relative mobility (RM), i.e. the ratio of the distance of peak of the abnormal albumin to the peak of the 1 globin to the distance of the peak of normal albumin (An) to the peak of 1 globin, was 0.79. Thus, this abnormal albumin was the slow type of bisalbumin (As). The peak zone of the abnormal albumin accounted for 21.8% and 38.2% of total serum proteins and total albumin, respectively, whereas the peak zone of the normal albumin accounted for 35.3% of total serum proteins. The pigment-binding ratio (abnormal albumin/normal albumin) was 0.62 (Figure 1A). Agarose gel electrophoresis of the same serum sample did not show the abnormal albumin peak (Figure 1B).

The serum samples were collected from 8 members of the patient's family and analyzed by capillary electrophoresis. The results revealed 5 cases of bisalbuminemia including 3 males and 2 females and they were all the slow-type (As) of bisalbuminemia. The general information about the members of the family and the pedigree tree are shown in Table 1 and Figure 1C, respectively.

Hereditary bisalbuminemia is a rare, autosomal and incomplete dominant hereditary condition. In most cases, bisalbuminemia is characterized by the presence of two distinct peaks of serum albumin on electrophoresis profiles. Homozygous allele of bisalbuminemia had also been found in very few cases, which displayed a single albumin band but its mobility in electrophoresis was different from

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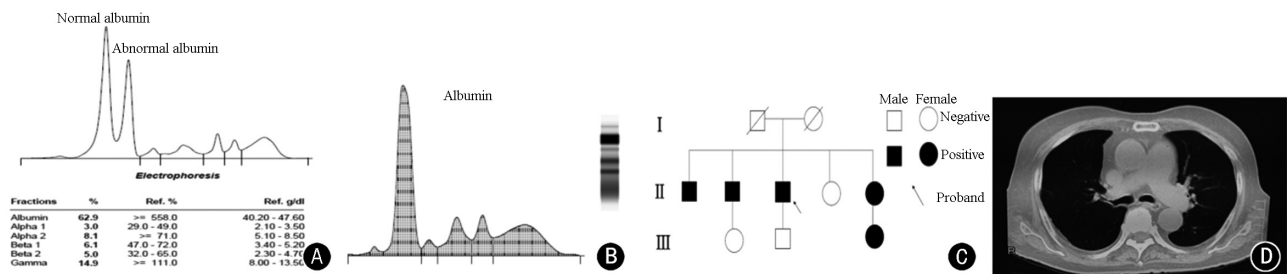


Figure 1. A: The capillary electrophoresis profile of the patient’s serum protein. B: The agarose gel electrophoresis profile of the patient’s serum protein. C: Pedigree tree of the patient’s family. D: Thorax CT of the proband patient.

Table 1. General information about the family with bisalbuminemia

Patients	Sex	Age (years)	Normal albumin/total protein (%)	Abnormal albumin/total proteins (%)	Relative mobility (RM)	Pigment-binding ratio
Proband	Male	44	35.3	21.8	0.79	0.62
Patient 1	Female	63	38.9	24.0	0.77	0.62
Patient 2	Male	54	37.9	24.9	0.80	0.66
Patient 3	Male	46	41.0	26.4	0.78	0.64
Patient 4	Female	25	37.3	25.2	0.78	0.68

that of the normal albumin. Based on the electrophoresis mobility of albumin, bisalbuminemia can be classified into normal type (A), fast type (Af) and slow type (As). To date, the reported cases of bisalbuminemia in China were almost the As type. For the case reported here, the agarose gel electrophoresis profile of the serum proteins revealed no distinct two peaks of albumin whereas capillary electrophoresis (CZE) of the same serum sample clearly revealed two distinct peaks, this disparity may be related to the fact that the 12 fragments of albumin can be more easily separated by capillary electrophoresis,⁴ and thus, capillary electrophoresis has a higher diagnostic sensitivity. The inconsistent results obtained with both electrophoresis methods were also reported by other investigators.⁵

We performed capillary electrophoresis with the serum samples collected from 8 members of the patient’s family and found that 5 members had bisalbuminemia, consistent with the genetic rules of genetic diseases. It had been reported from other studies that the incidence of hereditary bisalbuminemia was approximately 0.03%. Some diseases such as hyperthyroxinemia, hypoproteinemia, diabetes and even hematologic malignancies were reported to be accompanied with bisalbuminemia. Because a majority of patients with bisalbuminemia were identified randomly during the routine biochemical tests and these patients always had some types of chronic diseases, it is very difficult to determine the precise relationship between bisalbuminemia and these diseases.

We used the key word “bisalbuminemia” to search for the relevant literatures in the China National Knowledge Infrastructure (CNKI) database and Wanfang Database and found a total of 125 patients from 20 families including 4 individual cases in China had been reported by August 2013. When we used both key words “bisalbuminemia” and “ABPA” to search the relevant literatures in Pubmed database, no reports about the coexistence of bisalbuminemia with ABPA was found by August 2013,

which indicate that perhaps this is the first report about the coexistence of bisalbuminemia with ABPA in the world. ABPA is an adaptive lung disease characterized by an exaggerated response of the immune system to fungus *Aspergillus*, whose symptoms include difficult-to-control asthma, abnormal increased levels of total serum IgE and the specific IgE, and dilatation of the bronchial tubes, according to whether patients are associated with central bronchiectasis or not. ABPA has two subtypes, i.e. ABPA-CB (ABPA with central bronchiectasis) and ABPA-S (ABPA without central bronchiectasis). The abnormal increased total serum IgE level (>700 kU/L) and the *Aspergillus*-specific antibody (SIgE) level are the important criteria for diagnosis of *Aspergillus*-related asthma. As for the patient in this study, while the SIgE was monitored negatively when admitted to our hospital, considering that the patient had 1.5 years of case history of recurrent asthma and was given systemic hormonal therapy repeatedly, these factors could affect the measured value for SIgE criterion. Based on the typical symptoms, the significant high level of total serum IgE, the positive result of *Aspergillus* antigen intradermal test and the lack of central bronchiectasia in thorax CT (Figure 1D), this patient was finally diagnosed as ABPA-S. It has been demonstrated that genetic susceptibility may play an important role in the pathogenesis of ABPA. Whether or not bisalbuminemia is associated with ABPA requires further confirmation. Due to the limited availability of research facility in our laboratory, a genetic analysis for the abnormal albumin was not performed.

It has been known that the serum albumin is the major carrier of a number of lipophilic hormones such as steroid hormones, thyroid hormones and prostaglandins and thus, is involved in the regulation of the available hormones to interact with their corresponding receptors. The generation of abnormal albumin is a consequence of mutations of albumin gene, which leads to structural changes of the key amino acid residues. A majority of point mutations

are mainly distributed and concentrated on the surface of albumin molecule and a few point mutations are found in its ligand binding sites. It has been known that substitution of Leu90 and Arg242 of human albumin causes strong binding of triiodothyronine and l-thyroxine, respectively, leading to two clinical syndromes. Furthermore, due to liver's strong compensatory ability, these mutations may not significantly affect the biological functions of albumin. However, when the amount of the mutant albumin reaches enough levels, the abnormal albumin may affect the normal physiological functions of albumin including its capacity of binding to these hormones. In this study, we found that the amount of abnormal albumin in the serum samples of the patient and other members of his family was as high as 20% to 25% of total albumin, thus the amount of glucocorticoids and other hormones carried by normal albumin patients might be reduced and could not meet the normal physiological need. Thus, supplementation of exogenous glucocorticoid was required, leading to the hormone-dependent symptoms. However, this hypothesis requires further study.

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