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Review

Congenital analbuminaemia: Molecular defects and biochemical and clinical aspects☆

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ABSTRACT

Background: DNA and mRNA sequencing of the coding regions of the human albumin gene (*ALB*) and of its intron/exon junctions has revealed twenty-one different molecular defects causing congenital analbuminaemia (CAA).
Scope of review: To describe the mutations in molecular terms and to present the current knowledge about the most important biochemical and clinical effects of CAA.
Major conclusions: CAA is rare, but its frequency seems to be significantly higher in restricted and minimally admixed populations. The condition affects especially the lipid metabolism but apart from a possible increased risk for atherosclerotic complications, it is generally associated with mild clinical symptoms in adults. By contrast, several reports indicate that analbuminaemic individuals may be at risk during the perinatal and childhood periods, in which they seem to show increased morbidity and mortality. The twenty-one causative defects include seven nonsense mutations, seven changes affecting splicing, five frame-shift/deletions, one frame-shift/insertion and one mutation in the start codon. These results indicate that the trait is an allelic heterogeneous disorder caused by homozygous (nineteen cases) or compound heterozygous (single case) inheritance of defects. Most mutations are unique, but one, named Kayseri, is responsible for about half of the known cases.
General significance: Study of the defects in the *ALB* resulting in CAA allows the identification of "hot spot" regions and contributes to understanding the molecular mechanism underlying the trait. Such studies could also give molecular information about different aspects of *ALB* regulation and shed light on the regulatory mechanisms involved in the synthesis of the protein. This article is part of a Special Issue entitled Serum Albumin.

1. Introduction

The major human blood protein, serum albumin (ALB), is encoded on chromosome 4q13.3 by a single-copy autosomal gene (*ALB*; NCBI Reference Sequence: NG_009291.1). The gene is composed of 15 exons, the last of which is untranslated [1]. It is expressed in a codominant manner, i.e., both alleles are translated. In liver cells, the messenger RNA (NCBI Reference Sequence: NM_000477.5) encodes a precursor protein (preproalbumin) of 609 amino acid residues (NCBI Reference Sequence: NP_000468.1). Cleavage of the 18-residue signal peptide and of the 6-residue propeptide yields mature ALB, which consists of a single unglycosylated chain of 585 amino acids with a molecular mass of 66.5 kDa. The protein is secreted into the blood stream, where it accounts for 60%–65% (reference range 35–45 g/L) of total serum proteins [2]. One of its main functions is to act as a transport and depot protein for a wide variety of endogenous ligands such as fatty acids, hormones, steroids, bilirubin, and heme. ALB can also bind heavy metal ions and exogenous ligands such as many drugs, which is why a decrease in its serum level can have important pharmacokinetic consequences. Another important function is based on its high intravascular concentration (ca. 0.6 mM), which enables the protein to play a critical role in exerting colloid osmotic pressure and thereby to maintain the oncotic pressure and volume of blood [2]. In addition, the protein is a circulating antioxidant [3], and it has enzymatic properties [4]. Finally, because of the protein net charge of ca. −15 at physiological pH, it is important for the Donnan effect in the capillaries.

ALB exhibits a significant degree of DNA polymorphism [5]. Mutations may cause the presence of two circulating forms of the protein (bisalbuminaemia or alloalbuminaemia) (see [6] — 2013-this issue) or result in the absence of the protein from the blood (analbuminaemia). Many observations propose the existence of an important link between the concentration of ALB and health, which is why it has been suggested that ALB is an essential protein. Therefore, it is surprising that analbuminaemic individuals can survive with only

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minor clinical effects. Congenital analbuminaemia (CAA, MIM 103600) is rare, but it is probably more common than widely assumed, because affected individuals may succumb in the foetal state or early infancy, if they are not able to compensate for the missing ALB through an increased synthesis of other plasma proteins, which partly can take over the lacking ALB functions [7].

In this review, we have tabulated the twenty-one currently known mutations of the *ALB* which result in CAA. We also describe the mutations in molecular terms and discuss the biochemical and clinical effects of the condition.

2. Frequency and clinical and biochemical signs

CAA can be defined as a condition characterised by an ALB concentration of <1 g/L or identified by genetic studies of the *ALB*. It is very rare, since its prevalence is estimated at less than 1 in 1 million, apparently without gender or ethnic predilection [8]. The frequency of the trait seems to be significantly higher in restricted and minimally admixed population groups than in the average population. Examples are two First Nation communities of Cree descent living in the northwestern central plains of Saskatchewan (Canada) [9] and a Slovak gypsy settlement (S. Rosipal, personal communication). The first case of CAA was described in 1954, when H. Bennhold et al. reported the surprising finding of no detectable ALB, when serum from a 31-year old German woman field worker was examined by electrophoresis. She had oedema to a slight degree and was fatigued but otherwise not obviously ill [10]. After this first finding, only some fifty cases have so far been described world-wide; they are listed in the continuously updated Register of Analbuminaemia Cases [8]. The reported cases are from 1 week to 62 years of age with surprising mild or no symptoms.

The half-life of ALB is ca. 19 days, and its rate of synthesis and secretion from the liver is ca. 14 g daily in a healthy, adult person [2]. Having a normal ALB concentration seems to be important, because an association between hypoalbuminaemia and mortality has been widely reported for patients with various diseases such as acute heart failure, chronic and end-stage renal disease, different cancer forms, stroke, hip fracture, pneumonia, dementia, haemodialysis and peritoneal dialysis [11–16]. Often the association is so strong that the ALB concentration can be used as an independent prognostic predictor [13–16]. By contrast, normal or higher ALB levels are protective against coronary heart disease and many disease conditions of the brain [17,18]. An association between ALB concentration and mortality has also been found in community-dwelling populations. Thus, several studies of subjects with ages of 60 or more have shown that lower ALB levels are an independent prediction of total mortality [11].

Despite the many and important roles of ALB, a life-long absence of the major blood protein does not result in a severe phenotype in adults. As reported in the Register of Analbuminaemia Cases, analbuminaemic individuals have few clinical symptoms of their condition other than mild oedema, hypotension, fatigue and, occasionally, a peculiar lower-body lipodystrophy (mainly in adult females), whilst the most common biochemical findings are increases in non-albumin protein levels and hypercholesterolaemia.

3. Adaptation to life without albumin

It is not fully understood why the almost complete absence of ALB causes only few biochemical effects and clinical symptoms. The most important compensatory mechanism is an increase in the synthesis of other serum proteins, of which the lipoproteins may assume many of the transport functions of ALB. In this way, the total serum protein level is only marginally decreased in most analbuminaemic individuals [19]. CAA is usually not associated with systemic oedema most probably because of the above-mentioned compensatory increase in other plasma proteins, and because of a tendency of the analbuminaemic individuals to have low oncotic blood pressure or low normal blood pressure [2]. Amongst the non-albumin proteins, a significant increase was observed in the serum level of apolipoprotein B-100, that takes over most of the fatty acid transport, one of the essential transport functions of ALB [19]. The pathophysiology of the important hyperlipidaemia usually observed in analbuminaemic subjects, with a significant increase in the total and LDL-cholesterol levels, but normal levels of HDL-cholesterol and triglycerides, is probably also linked to the increase of serum apolipoprotein levels, especially of apolipoprotein B-100 [19]. Hepatic production of precursor lipoproteins in response to the reduced colloid osmotic pressure has been advanced as one important effector mechanism, but the factors that determine the phenotype of dyslipoproteinaemia and the primary stimulus for hypercholesterolaemia are not completely understood [20,21].

The hyperlipidaemia often results in lipodystrophy which is a condition characterised by severe obesity of the thighs and lower extremities, whereas the upper body appears normal [2]. It was reported as the cause of abnormal body habitus occurring in about one-third of post-pubertal analbuminaemic females [22]. The lack of ALB can result in lipodystrophy in two different ways. When the long-chain fatty acids are cleaved from circulating lipoproteins by lipoprotein lipase in capillary walls, the free fatty acids are more prone to enter the adipose tissue in the absence of ALB as a recipient. Furthermore, the oedema of the lower extremities, attributable to the lower serum protein level, slows the return circulation from the legs, making it more likely that adipose tissue will form there [2].

In addition to fatty acids, binding of other ligands such as ions and hormones is altered in CAA. For example, normally ca. 45% of total serum calcium is bound to ALB. Consequently, analbuminaemic individuals are expected to have a reduced protein-bound fraction of calcium and hence a low total serum calcium concentration, often below the normal range [22]. However, the levels of free, active calcium are normal, and clinical symptoms of hypocalcaemia have never been reported in adult analbuminaemic individuals [19]. On the other hand, however, the protein-bound fraction of L-thyroxine seems to be increased in some cases of CAA. This is due to a compensatory increase in the concentration of thyroxine-binding globulin, which has a higher affinity for L-thyroxine than does ALB. The increased binding results in an increase in total L-thyroxine levels, whereas the free fraction of the hormone is normal [19]. However, clinical mild primary hypothyroidism was reported in 2 other cases, which were treated with L-thyroxine [23,24].

Perinatal jaundice in newborns with CAA has not been described, even though the serum of an analbuminaemic child was suggested to have only about 25% of normal binding capacity for bilirubin, as determined by a bromophenol blue binding assay [25]. In normal pharmacological situations ALB is the major binding protein for both diazepam and warfarin. Accordingly, the unbound fraction of these representative drugs was approximately 10-fold the normal level in this child, causing higher peak activity, earlier onset of toxicity and twice-quicker clearance [25]. These examples could indicate significant pharmacodynamic consequences of CAA in general and show a more rapid onset of drug action, a greater peak response, and an earlier appearance of toxicity [25]. In this connection it is of interest to note that the total concentration of clofibrate in plasma is much lower, but its free concentration is higher, in Nagase analbuminaemic rats as compared to normal ones given the same drug doses [26]. Such changes could lead to adverse effects, perhaps even toxicities, of drugs. In view of the altered pharmacokinetics in analbuminaemic individuals, albumin-bound drugs should be administered with caution and monitored carefully [19].

The relatively few data available in the literature propose that individuals lacking ALB can live fairly normal lives, including parenting of children, and their longevity appears not to be significantly affected [5,8]. Although CAA is thought to be associated with few medical symptoms, an open question is whether analbuminaemic individuals are at risk for developing atherosclerotic complications. Hypercholesterolaemia may have been responsible for some cases of premature coronary heart