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Review Article

Overview of Acute Phase Proteins: Types, Pathogenesis and Clinical Significance

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Abstract: Acute-phase proteins (APPs) are a class of proteins whose concentrations in blood plasma either increase (positive acute-phase proteins) or decrease (negative acute-phase proteins) in response to inflammation. This response is called the *acute-phase reaction* (also called *acute-phase response*). The acute-phase reaction characteristically involves fever, acceleration of peripheral leukocytes, circulating neutrophils and their precursors. The terms *acute-phase protein* and *acute-phase reactant* (APR) are often used synonymously, although some APRs are (strictly speaking) polypeptides rather than proteins. These proteins serve as inhibitors or mediators of the inflammatory processes and include C-reactive protein, α_1-acid glycoprotein, haptoglobin, mannose-binding protein, fibrinogen, α_1-antitrypsin, and complement components C3 and C4. The concentration of these acute phase proteins usually increases during inflammation, whereas the concentration of prealbumin and albumin (also acute phase proteins) decreases in inflammation. Once concentrations of acute phase proteins and systemic concentrations of inflammatory cytokines are elevated, they affect the heart rate, blood pressure, and the hypothalamic regulation of temperature by directly or indirectly stimulating neurons within specific hypothalamic nuclei. These changes also affect respiratory rates and gaseous exchange.

Keywords: Acute Phase Proteins, Types, Pathogenesis, Clinical significance.

INTRODUCTION

The acute phase response is a facet of the innate immune system that occurs in response to infection, trauma or other insults. Certain mediators, known as acute phase reactants, are increased or decreased in the context of acute inflammation. These markers are commonly measured in clinical practice as indicators of acute illness. An acute phase reaction classically presents with fevers, rigors and tachycardia.

❖ **Types of Acute-phase Proteins:**

➢ **Positive acute phase reactants** are those whose concentration increases with inflammation. These include:

- C-reactive protein (CRP)
- Fibrinogen
- Ferritin
- Hepcidin
- Haptoglobin
- Caeruloplasmin
- Complement proteins C3 / C4
- Serum amyloid A (not measured)

➢ **Negative acute phase reactants** are those whose concentrations decrease in an acute phase response. These include:

- Serum albumin
- Transferrin
- Alpha-foetoprotein

❖ **Pathogenesis:**

The acute phase response is predominantly mediated by the pro-inflammatory cytokines tumour necrosis factor (TNF), interleukin 1 (IL-1) and interleukin 6 (IL-6) secreted by macrophages and other immune cells.

❖ **Causes of Acute Phase Response:**

- **Infection** - bacterial, viral, fungal, parasitic
- **Tissue infarction** - e.g. myocardial infarction, renal infarction, splenic infarction, acute limb ischaemia
- **Exogenous substances** (i.e. foreign bodies)
- **Endogenous substances** - uric acid crystals, calcium pyrophosphate crystals
- **Autoimmune disease**
- **Allergies**
- **Neoplasia**
- **Trauma**
- **Surgery**
- **Burns**

❖ **Role of APRs:**

They have a wide range of activities that contribute to the host defense. APRs have various antimicrobial and anliinflanunacory activities (e.g. complemem factors). Metal binding proteins can chelate various metals such as iron, copper making them unavailable for the bacteria.

❖ **Importance of Various Acute-phase Proteins:**

➢ **C-Reactive Protein:**

C-reactive protein is an acute phase protein that is involved in innate immunity, and is responsible for activating the complement pathway. Serum CRP rises rapidly, with a maximal concentration reached within two days; it falls quickly once inflammation has resolved. CRP has little efficacy as a screening tool for inflammation, however the trend in CRP is useful for monitoring resolution or progression of an inflammatory process.

The normal level of CRP is less than 0.2mg/dl. However, it increases by several folds in acute inflammatory conditions.

- **Insignificant increase of CRP (<1 mg/dl):** It occurs in conditions such as heavy exercise, common cold and pregnancy.
- **Moderate increase (1- 10 mg/dl):** It occurs in conditions such as bronchitis, cystitis, malignancies, pancreatitis, myocardial infarction.
- **Marked increase of CRP (> 10 mg/dl):** It occurs in conditions .such as acute bacterial infections, major trauma and systemic vasculitis.

➢ **Ferritin:**

Ferritin is an intracellular iron storage protein whose levels are indicative of the body's total iron stores. An elevated ferritin is classically a marker of iron overload, however ferritin is also an acute phase reactant and may be elevated in the context of acute inflammation.

➢ **Procalcitonin:**

Procalcitonin is a protein normally produced by the thyroid; it is secreted by extrathyroid tissue in the context of infection or inflammation. Procalcitonin rises rapidly with maximal concentration reached within two days, and falls quickly once inflammation has resolved.

➢ **Haptoglobin:**

Haptoglobin is an alpha-2 glycoprotein secreted mainly by the liver that binds plasma free haemoglobin. Haptoglobin is primarily used as a marker of intravascular haemolysis, in which its level will reduce.It is also an acute phase reactant, however, and haptoglobin will be increased in the presence of infection, inflammation or malignancy.

➢ **Fibrinogen:**

Fibrinogen is a coagulation factor that is converted to fibrin and is essential for the formation of a clot. Inflammation and coagulation are tightly linked, and as such the fibrinogen level will rise in the presence of acute inflammation.

➢ **Erythrocyte Sedimentation Rate:**

The erythrocyte sedimentation rate (ESR) is a measure of the number of red bloods cells that precipitate in a tube over an hour. ESR is a surrogate for the fibrinogen, as erythrocyte sedimentation occurs in the context of hyperfibrinogenaemia. An elevated ESR is classically used as a marker of chronic inflammation.

➢ **Caeruloplasmin:**

Caeruloplasmin is a copper-containing protein that may be measured for use as an inflammatory marker, however it is very uncommonly used in this fashion.

➢ **Albumin:**

Albumin is a negative acute phase reactant, meaning that its level will fall in the context of acute inflammation. This occurs as a result of reduced hepatic production, as well as proteolysis.

Important differential diagnoses for reduced albumin include malnutrition, liver disease and protein loss (nephrotic syndrome, protein-losing enteropathy, severe burns)

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