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The Influence of Complement Cascade on The Ups and Downs of Bipolar Disorder

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Abstract:
Bipolar disorder patients have recently been shown to exhibit increased levels of certain complement component and decreased in others, studies have been made on patient to evaluate their serum levels of these components and link their function to the pathogenesis of Bipolar Disorder. Regardless to the disagreement of the studies involved, a similar result is approached.

Introduction:
Bipolar disorder is a brain disorder associated with impaired neurogenesis that causes unusual shifts in mood, energy, activity levels and the ability to carry out day-to-day tasks. Although the etiology is still uncertain but couple of studies on Bipolar disorder patients have shown the clear role of complement cascade system in the pathogenesis of all types of bipolar disorder.

Types of Bipolar disorder:
There are 4 types of bipolar disorder classified as below:
Bipolar I Disorder: is mainly defined by mixed episodes that last at least seven days, or by manic symptoms that are so severe that the person needs immediate hospital care. The person also has depressive episodes lasting at least two weeks leading to a change in the person's normal behaviour.

Bipolar II Disorder: is defined by a pattern of depressive episodes shifting but with no mixed episodes.

Bipolar Disorder Not Otherwise Specified (BP-NOS): is diagnosed when a person has symptoms of the illness that do not meet diagnostic criteria for either bipolar I or II. The symptoms may not last long enough, or the person may have too few symptoms, to be diagnosed with bipolar I or II. However, the symptoms are clearly out of the person's normal range of behaviour.

Cyclothymic Disorder or Cyclothymia: is a mild form of bipolar disorder. People who have cyclothymia have episodes of hypomania that shift back and forth with mild depression for at least two years. [1]

Functions of the complement system:
The complement system has a variety of functions in various areas of the body, its mostly known for its role in the innate immunity that enhances complements ability of antibodies and phagocytic cells to clear microbes and damaged cells from an organism, promotes inflammation and attacks the pathogen's cell membrane. in addition it plays an important role in processes such as: Reducing inflammatory reaction, removal of apoptotic cells, angiogenesis, wound healing, repair processes and the mobilization of some types of stem cells. It is also considered to play a role in the pathogenesis of neurodegenerative diseases. [2]

Discussion:

hypothalamic-pituitary-adrenal axis:

Bipolar disorder has a multifactorial etiology (genetic and environmental factors), but recent studies have been focusing on the consequences of aberrant immune-inflammatory processes on the brains activity. It appears that activation of inflammatory processes within the central nervous system and systemic inflammatory reactions lead to an increase activity of the hypothalamic-pituitary-adrenal axis which is a complex set of direct influences among three components: the hypothalamus, the pituitary gland and the adrenal that controls reactions to stress and regulates the immune system, mood, emotions and energy storage. This activation of the hypothalamic-pituitary-adrenal axis occurs especially in the manic phase (a state of intense excitement and happiness) causing anti-inflammatory steroids e.g. cortisone to be produced, this will result in behavioural changes leading to energy conservation such as increased sleep and reduced appetite.[3] All of this, instead of stabilizing the patients mood, putting them in a well mental state, however will get them in a depressive episode, which sums up the medical condition Bipolar disorder.

Complement Cascade:

Most inflammatory mediators have few actions in healthy CNS tissue and are expressed at very low, However they are induced rapidly in response to tissue injury or infection and have many actions. A communication between the CNS neural tissue with the immune system can occur through leakages within the blood-brain barrier by probably either active transport or through leaky regions of endothelia when a pathological condition is present, this happens during the periods of Bipolar disorder episodes and therefore a cross-talk between the central nervous system and the immune system may be facilitated. . It has been shown that after several hours from such a leakage, complement components may penetrate the brain tissue. It is believed that the permeability of the BBB can further progress in with Bipolar disorder episodes. For these reasons, increased concentrations of C3a and C5a in patients with Bipolar disorder may significantly affect the central nervous system, including the regenerative processes. [3]

The Complement system has a regenerative role. It consists of proteins produced mainly in the liver and in small amounts also by neurons, microglia, astrocytes and oligodendrocytes. Component C3a affects neurogenesis, stimulates the differentiation of neural progenitor cells under hypoxic conditions. It also modulates astrocytes (control of the blood brain barrier and blood flow) response to ischemia, increasing their ability to survive stress conditions associated with ischemia. The presence of the receptors C5aR C3aR on neurons can prevent their apoptosis, while the activated complement is involved in a process called synaptic elimination, it enhances the secretion of proinflammatory cytokines by glial cells and induces neuronal damage

and death by C5b-9 (complement membrane attack complex), also the C5a component has a neuroprotective effect on mature neurons.[2]

A study that included an evaluation concentrations of C3a, C5a, and C5b-9 complement cascade components in the peripheral blood of 30 patients suffering from bipolar disorder for at least 10 years, BD type I (BD-I, 22 persons), and BD type II (BD-II, 8 patients).[2]

The result was compared to healthy controls, BD patients had elevated concentrations of all the investigated components, however in patients with BD-II, a higher concentrations of C5b-9 was seen as compared to patients with BD-I.[2]

Increased concentrations of components C3a and C5a of the complement system in the affected group as compared to healthy controls is a clear sign of involvement of the complement cascade in the pathogenesis of BD and provides further evidence of immune system dysregulation in BD patients. [2]

The activation products of the cascade contribute to the production of other inflammatory mediators, and can therefore promote tissue injury at sites of inflammation. The most potent proinflammatory molecules produced in response to complement activation are the anaphylatoxins C3a and C5a, which exert their actions through specific receptors. Activation of the complement system also leads to formation of the membrane attack complex (MAC), which lyses target cells by forming a pore in the phospholipid bilayer. Neurones, microglia, astrocytes and oligodendrocytes express complement proteins, and neurones are particularly susceptible to complement-mediated damage. Many of the same inflammatory mediators increase in chronic neurodegenerative diseases: activation of microglia leads to production of cytokines, superoxide radicals, NO and components of the complement system. [3]

Other studies on patients showed decreased levels of all investigated components, namely C3a, C5a, and C5b-9.[4] On the other hand, in a study examining concentrations of C4 and sC5b-9 (soluble C5b-9, found lower concentrations of these components in patients with chronic BD, both in the acute and chronic phase, compared to healthy controls and individuals with the first episode of mood disorders in the course of BD.[2]

Both studies make perfect sense although they scientifically disagree, the first study shows that increased levels of the investigated complement component will form what is known as the membrane attack complex which will attack brain cells and lead to a chronic neurodegenerative disease (bipolar disorder). However the other two studies proved a decrease in the investigated complement component, the low amount of complement will cancel out in other words limit their neuroprotective function leading to the apoptosis of brain cells.

Conclusion:

The complement cascade plays a significant role in the pathogenesis of Bipolar Disorder. An activation of inflammatory processes is achieved by the action of the increased complement components (the membrane attack complex) which lyses target cells causing the chronic neurodegenerative disease in addition to the activation of the hypothalamic-pituitary-adrenal axis that shifts the patient from the manic phase to the depressive phase. Deficiency of the complement component will impair neurogenesis and lead to the manifestations of Bipolar disorder.

References:

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