CYREX® Laboratories

CLINICAL SPECIFICATIONS

BLOOD-BRAIN BARRIER PROTEIN

Function:

The BBB protein is a glial-specific protein that is expressed primarily by mature astrocytes that sheathe the blood vessels. This protein functions not only in protection of the barriers but also has a role in neurite extension. It acts in developing neurons as a neurotrophic factor and neuronal survival protein. Thus, antibody production against it may indicate not only damage to the astrocytes but also the prevention of its functionality as a nerve growth factor.

Associated With:

Traumatic brain injury[1]
CNS involvement in lupus[2]
Sarcoidosis[3]
Neurosarcoidosis[3]
Lost tolerance to environmental triggers[4,5]

Known Cross-Reactions:

$A\beta_{42}$ peptide[6]

Clinical Significance:

When the BBB is inflamed, the tight junctions open and produce a condition called increased BBB permeability, which is also increasingly referred to as "leaky brain" (not the same as leaky brain syndrome). In this condition, xenobiotics, viruses, bacterial toxins and other molecules greater than 400 daltons in size, which are normally excluded, can penetrate the BBB.[5] Penetration of the BBB by very large molecules such as bacterial endotoxins such as lipopolysaccharides (LPS) and cytolethal distending toxins (CDTs), or even intact viruses, may first cause neuroinflammation, followed by neuroautoimmunity with peripheral or central nervous system (CNS) symptoms.[4,7] Disruption of the brain barrier results first in the release of BBB and tight junction proteins and then in the formation of IgG, IgM or IgA antibodies against them.[8] Production of these antibodies against the BBB and other neural cell antigens from a cell-mediated and humoral immune response may indicate a pathological alteration of the protective brain barrier.[2,9] Continued opening of the BBB and the persistent release of autoantigens for an extended period in adulthood may cause neuronal cell death and an early cognitive decline. Repeated head trauma and traumatic brain injury (TBI) associated with accidents and some sports, such as football or hockey, have also been shown to damage the BBB and the astrocytes that protect the BBB from the brain side.[8] TBI is a multifaceted pathology involving excitotoxicity, free radical formation, brain swelling, and the entry of locally produced molecules such as cytokines, chemokines, and other molecules.[1] For an excellent review on the role of the BBB in health and neurodegenerative disorders including AIDS dementia, Alzheimer's, Amyotrophic Lateral Sclerosis, Multiple Sclerosis and Parkinson's, please see Zlokovic.[10]

References:

1. Vojdani. Brain-reactive antibodies in traumatic brain injury. Funct Neurol Rehabil Ergon, 2013; 3(2-3):173-181.
2. Meroni. Endothelium and the brain in CNS lupus. Lupus, 2003; 12(12):919-928.
3. Tsukada, et al. Endothelial cell damage in sarcoidosis and neurosarcoidosis: autoantibodies to endothelial cells. Eur Neurol, 1995; 35(2):108-112.
4. Hanin. The gulf war, stress and leaky blood-brain-barrier. Nature Med, 1996; 2(12):1307-1308.
5. Zheng, et al. Brain barrier systems: a new frontier in metal neurotoxicological research. Toxicol Appl Pharmacol, 2003; 192:1-11.
6. Vojdani and Vojdani. Amyloid-beta 1-42 cross-reactive antibody prevalent in human sera may contribute to intraneuronal deposition of A-beta-P-42. Int J Alzheimers Dis, 2018; 2018:1672568.
7. Friedman et al. Pyridostigmine brain penetration under stress enhances neuronal excitability and induces early immediate transcriptional response. Nature Med, 1996; 2(12):1382-1395.
8. Marchi et al. Consequences of repeated blood-brain barrier disruption in football players. PLoS ONE, 2013; 8(3):e56805.
9. Sternberger and Sternberger. Blood-brain barrier protein recognized by monoclonal antibody. Proc Natl Acad Sci USA, 1987; 84:8169-8173.
10. Zlokovic. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron, 2008; 57:178-201.

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CLINICAL SPECIFICATIONS

CLAUDIN-5

Function:

Claudin-5 is a major cell adhesion molecule of tight junctions in brain endothelial cells. Claudin works in conjunction with other tight junction structures such as occludin, zonulin and junctional adhesion molecules to tie endothelial cells together, which forms the blood-brain barrier (BBB). By allowing only the entry of necessary nutrients and stopping macromolecules, tight junctions ensure the prevention of antigen invasion into the brain and nervous system.

Associated With:

Autism[1]

Known Cross-Reactions:

Clinical Significance:

The claudin family of proteins has many functions.[2] Claudin-5 is shown to play a role in sealing the blood-brain barrier structure.[3] Antibodies to Claudin-5 were found in patients with autism.[1] Amyloid beta (Aβ) has been shown to breach the BBB via the paracellular pathway; a correlation was seen between an increase in both Aβ levels in the brain and cognitive decline, and a suppression of claudin-5, occludin and other tight junction proteins in both mice and humans.[4, reviewed in 5] Autoreactive antibodies, antibodies made against environmental triggers such as dietary proteins or pathogens, constantly circulate in the blood stream. These autoreactive antibodies may cross-react with tissues in the brain and nervous system. As long as the BBB is intact, those autoreactive antibodies cannot harm the delicate brain and nervous system tissues. When the BBB is broken, these autoreactive antibodies, after reaching the brain, can trigger neuroinflammation, neuroautoimmunity and neurodegeneration. The more circulating autoreactive antibodies that cross the barriers, the more damage to the brain.[6] If a patient tests positive for the biomarkers of BBB permeability, such as BBB proteins, Claudin-5 and Aquaporin-4, it is essential to remove known cross-reactors (see Array 20 and Array 7 spec sheets) in order to prevent neurological damage in patients with Alzheimer's disease and improve the time and process of healing the BBB.

References:

1. Fiorentino et al. Blood–brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. Molecular Autism, 2016; 7:49.
2. Devaux et al. Claudin proteins and neuronal function. Curr Top Membr, 2010; 65:229-253.
3. Nitta et al. Size-selective loosening of the blood-brain barrier in claudin-5–deficient mice. J Cell Biol, 203; 161(3):653-660.
4. Keaney et al. Autoregulated paracellular clearance of amyloid-β across the blood-brain barrier. Sci Adv. 2015 Sep 4;1(8):e1500472.
5. Yamazaki and Kanekiyo. Blood-brain barrier dysfunction and the pathogenesis of Alzheimer's disease. Int J Mol Sci, 2017; 18:1965.
6. Vojdani. Brain-reactive antibodies in traumatic brain injury. Funct Neurol Rehabil Ergon, 2013; 3(203):173-181.

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