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Research Article,

The Reaction of Antibodies after Traumatic Brain Injury

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Abstract:

Immune system attacks on the body's own brain or neural tissues are known as neuroautoimmune diseases. The blood-brain barrier (BBB), which is made up of highly specialised brain endothelial cells, normally shields the brain from the outside world. However, recurrent disruptions to the BBB may result from traumatic brain injury (TBI), which can happen in sports like football and other ones. A faulty exchange of chemicals between the blood and the brain may result from this opening of the entrance to the brain. Various brain tissue antigens and BBB proteins, including S100-B, may be wrongly recognised as intrusive agents by a compromised immune system, which can also result in the production of autoreactive antibodies. Concussions or other brain injuries have been effectively confirmed using S100-B in combination with CT scanning. The presence of S100-B antibodies may even be used to gauge a patient's level of recovery and determine whether it is safe to resume normal activities since they go further to show that the BBB has been compromised and autoimmunity has been triggered against the brain cells. The significance of detecting antibodies against S100-B and other CNS autoantigens in the diagnosis and treatment of TBI patients is supported by these results.

Keywords: antibodies, traumatic brain damage, autoimmunity, Brain Injury.

Introduction:

7% of the global population is afflicted with autoimmune illnesses. Pathogenic TH1 cells, autoreactive TH17 cells, antibodies, and related chemicals assault the antigens of many tissues, including brain tissue, in these illnesses. About 3% of the general population has brain-reactive antibodies, but they cannot cause brain disease unless they get across the blood-brain barrier (BBB) [1]. Brain endothelial cells with a high level of specialisation and complete differentiation to the neurovascular system make up the BBB. One vessel corresponds to each neuron in the estimated more than 10 billion capillaries present in the human brain. The capillaries in the human brain have a total length of roughly 400 kilometres. The BBB isolates the neurons from numerous elements of the circulating blood together with microglia, astrocytic foot processes, and pericytes [2]. Because all soluble molecules larger than 400 Da cannot pass through endothelial tight junctions and astrocytic foot processes into the nervous system, B cells are not exposed to a variety of specific brain antigens expressed on neurons, oligodendrocytes, microglia, and astrocytes during immune maturation. Because of this, the immune system lacks a mechanism for the formation of regulatory T-cells to create tolerance for brain antigens [3]. However, a number of factors, including stress, infection (particularly bacterial endotoxins), toxic chemicals, medicines, certain medications, and, most significantly, traumatic brain injury (TBI), may damage the BBB either directly or indirectly by activating inflammatory signals [4–12]. Pathogenic TH1 and TH17 cells are alteredly

transported between the blood and the brain and, to a lesser extent, from the blood to the brain owing to the breakdown of the BBB caused by the disruption of tight junctions by different triggers. The abnormal angiogenesis, vascular regression, brain hyperfusion, neuroinflammatory reactions, injury to neural cells, and release of neural antigens into the blood are all possible outcomes of this molecular and cellular interchange between the blood and the brain [2]. These antigens will be conveyed by antigen-presenting cells, first to T cells and subsequently to B cells, resulting in brain-specific antibodies, as well as autoreactive TH1 and TH17 cells, due to abnormalities in immune tolerance or reaction to numerous neural antigens. In neuroimmune and neurodegenerative diseases such multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Alzheimer's, and Parkinson's disease, the entrance of these pathogenic cells and antibodies into the brain tissue may cause progressive synaptic and neuronal dysfunction and death [1,13]. In some circumstances, it may be reasonable to anticipate that brain antibodies that develop in diseases with obvious antigenic triggers, such as bacterial endotoxins or lipopolysaccharides (LPS), dietary antigens (gluten, milk proteins, excessive salt), and environmental toxins (heavy metals, polychlorinated biphenyls), will disappear once the inciting triggers are gone [4-12,14,15]. Therefore, eliminating the external triggers may lead to BBB repair and therefore the cessation of autoantibody synthesis. This may not be the case, however, in cases of recurrent TBI or brain trauma.

Changes in central nervous system in response to traumatic brain injury:

Excitotoxicity, the production of free radicals, brain swelling, and the entrance of locally generated molecules including cytokines, chemokines, and other molecules that might interfere with metabolism and cause neuroinflammation are all components of the complicated disorder known as TBI [16–18]. Given that 4 million Americans suffer from sports- and recreation-related concussions each year in the United States, it is becoming more and more crucial to comprehend the many processes involved in TBI [12,19,20]. In addition to a leaky BBB after TBI, the central nervous system also experiences a series of biochemical, immunological, and excitotoxic processes that are mediated by the innate and adaptive immune systems (CNS). Acute microglial activation sets off these excitotoxic events, which are then followed by the large release of glutamate and aspartate, which overstimulates glutamate receptors. As a consequence, calcium channels open, calcium enters the system, which causes neuronal toxicity and cell death [13,21]. This excitotoxic response may become better in a few hours or days, depending on the severity of the damage. 15% of the total glial cell population in the brain are microglial cells or resident macrophages. The CNS's primary active immune defence cells are these cells. Microglia are typically in a resting condition, but they have the ability to activate and shift into an active immune defence state in response to environmental stimuli, trauma or damage, BBB disruption, or disturbance of brain homeostasis. The host body releases immune factors, including chemokines and cytokines, reactive oxygen and nitrogen species, inflammatory prostaglandins, proteases, nitric oxide, and trophic factors, to help the healing process after an injury by removing the inciting agents and clearing dead or dying cells [21]. Nerve growth factors and brain-derived neurotrophic factors, which help to lessen neurotoxic processes in the brain and repair the damaged BBB, are among the neurotrophic and immunoregulatory or anti-inflammatory cytokines secreted by microglia during this healing process. Preventing further injuries before the brain is fully recovered is one of the main issues following a first damage. This is due to the fact that repeated brain damage that takes place before the neuroinflammatory response has fully healed and been repaired may hasten and increase chronic microglia activation, which can have detrimental effects. In fact, studies have demonstrated that after being partially activated, primed microglia completely express pro-inflammatory cytokines/chemokines and excitotoxins at levels that are substantially greater than those produced by the original damage. However, sometimes this typical protective microglial response to the damage does not have enough time to "turn off" the switching mechanism. In most circumstances, active microglia will flip to a reparative mode. It may cause neurodegeneration, persistent and severe brain immunoexcitotoxicity, and perhaps even neuroautoimmunities when the switching mechanism is stuck in the "on" state [12, 22]. The BBB's structural integrity has a significant impact on the neuroautoimmunity process. A BBB

disruption exposes a person to a variety of environmental stressors. Brain-reactive antibodies are seen in healthy persons without neurological symptoms due to the antigenic similarity of these triggers with neuronal cell antigens. Numerous neuroimmunological illnesses are impacted by these autoantibodies. Neuron-binding autoantibodies, for instance, have been found in the sera of patients with Alzheimer's disease, Sydenham's chorea, autism, multiple sclerosis, Guillain-Barré syndrome, Hashimoto's encephalopathy, lupus, chronic peripheral neuropathy, optic neuritis, vascular dementia, stiff person syndrome, and paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection [1]. In these circumstances, it seems that a compromised BBB gives these autoantibodies access to a number of targets on the surfaces of brain cells. Therefore, many neuroinflammatory and neurodegenerative disorders that entail BBB impairment may start or advance because of these antibodies.

Traumatic brain injuries occur every year in around 1 in 250 people, or 5% of all ER patients [23]. The amount of sub-concussive head blows in the National Football League has been calculated to be in the hundreds every season. Clinically, concussions may cause short- or long-term symptoms, lasting anything from a few minutes to many months. Numerous sportsmen have had to give up their sports due to severe post-concussive symptoms, some of which have been documented to endure for years in certain athletes. Football-related concussions are becoming more well known, but the underlying processes are still not fully understood. Seizures, Alzheimer's disease, stroke, and traumatic brain injury (TBI) have all been associated to BBB disruption (BBBD) or increased permeability of the brain vasculature [11]. When the BBB permits circulating autoantibodies to enter the brain, they have a pathogenic effect on the brain [24]. When BBBD is coupled with autoimmune reactivity, as in neuroautoimmune illnesses, the results might be harmful. In these situations, the loss of BBB integrity sets off a cellular and humoral immune response in the central nervous system (CNS) as well as the unmasking of CNS antigens, such as BBB proteins and S100-B astrocytic antigens, which in turn sets off peripheral immune responses against these antigens. A 21 kDa calcium-binding protein unique to glia, S100-B is mostly expressed on the endfeet of astrocytes. The BBB is made up of these endfeet and the tight junction proteins zonula occludens and ZO-1. Computed tomography (CT) scan is the standard technique for identifying intracranial damage in individuals with minimal injury. The CT scan is costly, exposes patients to high radiation doses, and only detects clinically meaningful lesions in fewer than 10% of cases [23], despite the fact that it has a high sensitivity for identifying intracranial damage in patients with brain injury. Because of this, the measurement of S100-B in blood was developed as a marker for both mild and severe brain damage [25,26]. S100-B protein levels in the blood were compared with CT scans and plasma S100-B levels in more than 2,000 patients in Bordeaux, France, as a screening tool for the early evaluation of small head injuries [23]. TBIs on CT scans were detected with a sensitivity of 99% and a specificity of 20% at a threshold of 0.12 microgram/L of S100-B [23]. Plasma S100-B in patients with mild head injury was shown to be a viable screening tool that may aid the physician in deciding without doing CT imaging [23]. The half-life of the S100-B 21 kDa protein is crucial to note since it explains why, in many players where S100-B was found, antigen levels reverted to pre-game levels within 24 hours of the game [23]. The rapid removal of 21 kDa from the blood may be due to an immunological response and the development of particular antibodies directed against S100-B. S100-B antibodies are far more stable in blood than the antigens themselves, with IgG having a half-life of 21 days. It is thus more beneficial to assess the antibodies to S100-B rather than merely the levels of S100-B in TBI.

Neuronal antigens:

Repeated "opening" of the BBB could cause immune cells to become activated against a brain antigen as a delayed pathogenic response. Self antigens are wrongly "recognised" by activated immune cells as foreign invaders, triggering an immunological response. However, other brain antigens, such as myelin basic protein (MBP), tau, and beta-trace protein, could also be attacked by the activated immune cells, leading to neuroautoimmunity. A very recent study

examined both the levels of S100-B and specific antibodies against S100-B in football players with TBI [11]. Although BBBD results in the production of antibodies, an autoimmune or neurological illness is not always indicative of the existence of neural autoantibodies in blood. Autoantibodies may actually be found in people who don't have any autoimmune symptoms [27]. However, autoantibodies may become pathogenic when they extravasate into cerebrospinal fluid from the subarachnoid space or when they enter the CNS via a BBBD [24]. As was previously mentioned, numerous autoimmune and/or neurological illnesses are linked to the existence or detection of autoantibodies. Numerous clinical disorders, including Alzheimer's disease, have been linked to increased antibody titers for S100-B and other brain proteins [28–30]. Epilepsy has also been linked to the presence of immunoglobulins in the brain [31]. According to recent studies, the existence of antibodies against S100-B is one of the early indicators of cognitive deterioration in senile dementia patients [28,29]. After repeated BBBDs in adulthood, the existence of an immunological response that lasts for a long time may result in neuronal cell death and an early cognitive impairment [32]. It has been suggested that some molecular "players" "swap teams" in the case of a BBBD, to use sports terminology [33]. Following a BBBD, certain serum molecules (albumin, magnesium ions, potassium ions, and immunoglobulins) may enter the brain and disturb the CNS's homeostasis. However, by unmasking an antigen, brain proteins may cause an autoimmune reaction. Football players who sustain head traumas have been shown to have a deterioration in cognitive function and an increased chance of acquiring neurodegenerative illnesses [30]. It should come as no surprise that autoantibodies to S100-B can be discovered in football players after playing even a single season, during which a typical player may experience 1,000 head hits or more [34]. If repeated head trauma causes BBBDs and results in the presence of autoantibodies in the CNS, this is to be expected. In a recent research including 67 football players, CT scans and tests to gauge balance, motor coordination, and memory were used to determine the amount of head impacts and brain damage [11]. Before and after football games, they took blood samples from 57 players and determined the amount of S100-B protein present. Players that had the most sub-concussive impacts had serum S100-B found in their blood. Large molecule S100-B (21 kDa) causes particular antibodies to be produced in response to even minute levels handled by immune system cells. The fact that this protein entered the blood indicates that the blood-brain barrier, or the biological entrance to the brain, was disrupted. As a result, the antibodies created in response to S100-B entered the brain and set off an autoimmune reaction against the brain tissue. In fact, a minority of athletes who did not have head concussions had an immunological response [11]. Given that concussions, which affect 40% of football players, may be challenging to diagnose, the discovery of antibodies against S100-B shows that there is not just an aberrant opening or door to the brain but also that autoimmune has been triggered against the brain cells. Additionally, increased levels of autoantibodies against S100-B and other brain tissue antigens such tubulin, cerebellum, synapsin, myelin basic protein, and myelin oligodendrocyte glycoprotein suggest recurrent sub-concussive episodes that are characteristic of BBBD. If these antibodies to S100-B and other brain tissue antigens are present or absent, it may be determined whether or not TBI or

Conclusion:

Concussion has happened; it can also tell us when it's safe to resume daily activities. Additionally, the persistence of white matter abnormalities seen by MRI and associated with cognitive impairments were predicted by serum levels of S100-B autoantibodies. The association between frequent BBB disruption and the probability of cognitive alterations in the future is supported by the linkage between serum S100-B autoantibodies and white matter abnormalities. The athletes may suffer recurrent BBB disruption and an increase in possible autoantigens in the blood even in the absence of a concussion. Microtubule-associated protein isoforms 5 and 7, neuromodulin 2, synapsin 1, beta-tubulin 3, and MBP were also shown to be autoantigens in the blood. Finally, it should be mentioned that although concussions and major blows are receiving a lot of attention, sub-concussive strikes that look to be damaging should also be of concern. These results provide credence to the idea that measuring antibodies to S100-B and other CNS autoantigens is crucial for correctly diagnosing and treating TBI patients. Cyrex Labs in Phoenix, Arizona is offering the

Neurological Autoimmune Reactivity Screen as their Array 7, which includes the detection of these brain-reactive antibodies.

References:

[1] Diamond B, Honig G, Mader S, Brimberg L, Volpe BT. Brain-reactive antibodies and diseases. Annu. Rev Immunol. 2013;31:345-385.

[2] Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron. 2008;57:178-201.

[3] Diamond B, Huerta PT, Mina-Osorio P, Kowal C, Volpe BT. Losing your nerves? Maybe it's the antibodies. Nat. Rev. Immunol 2009;9:449-456.

[4] Hanin I. The Gulf war, stress, and a leaky blood-brain barrier. Nat. Med. 1996;2(12):1307-1308.

[5] Friedman A, Kaufer D, Shemer J, Hendler I, Soreq H, Tur-Kaspa I. Pyridostigmine brain penetration under stress enhances neuronal excitability and induces early immediate transcriptional response. Nat. Med. 1996;2:1382-1385.

[6] Xaio H, Banks WA, Niehoff ML, Morley JE. Effect of LPS on the permeability of the blood- brain barrier to insulin. Brain Res. 2001;896:36-42.

[7] Hazleton JE, Berman JW, Eugenin EA. Novel mechanism of central nervous system damage in HIV infection. HIV/AIDS Res Palliat Care. 2010;2:39-49.

[8] Zheng W, Aschner M, Ghersi-Egea JF. Brain barrier systems: a new frontier in metal neurotoxicological research. Tox. App. Pharmacol. 2003;192:1-11.

[9] Seelbach M. Polychlorinated bishpenyls disrupt blood-brain barrier integrity and promote brain metastases formation. Env. Health Persp. 2010;118:479-484.

[10] Dietrich JB. Alteration of blood-brain barrier function by methamphetamine and cocaine. Cell Tissue Res. 2009;336:385-392.

[11] Marchi N, Bazarian JJ, Puvenna V, Janigro M, Ghosh C, Zhong J, Zhu t, Blackam E, Stewart D, Ellis J, Butler R, Janigro D. Consequences of repeated blood-brain barrier disruption in football players. PLoS One. 2013;8(3):e56805.

[12] Maroon JC, Lepere DB, Blaylock RL, Bost JW. Postconcussion syndrome: a review of pathophysiology and potential nonpharmacological approaches to treatment. Phys. Sportsmed. 2012;40:73-87.

[13] Calderon-Garciduenas L, Franco0Lira M, Mora-Tiscareño A, Medina-Cortina H, Torres-Jardon R, Kavanaugh M. Early Alzheimer's and Parkinson's disease pathology in urban children: friends vs foes responses – it is time to face the evidence. BioMed Res Int. 2013;Article ID 161687.

[14] Vojdani A, O'Bryan T, Kellermann GH. The immunology of gluten sensitivity beyond the intestinal tract. Eur. J. Inflamm. 2008;6(2):49-57.

[15] Vojdani A, Campbell A, Anyanwu E, Kashanian A, Bock K, Vojdani E. Antibodies to neuron- specific antigens in children with autism: possible cross-reaction with encephalitogenic proteins from milk, Chlamydia pneumoniae and Streptococcus Group A. J. Neuroimmunol. 2002;129:168-177.

[16] Pellman EJ, Lovell MR, Viano DC, Casson IR, Tucker AM. Concussion in professional football: neuropsychological testing – part 6. Neurosurgery. 2004;55:290–1303.

[17] Pellman EJ, Viano DC, Casson IR, Tucker AM, Waeckerle JF, Powell JW, Feuer H. Concussion in professional football: neuropsychological testing – part 4. Neurosurgery. 200455:290–1303.

[18] Neuwelt EA, Bauer B, Fahlke C, Fricker G, Iadecola C, Janigro D, Leybaert L, Molnár Z, O'Donnell ME, Povlishock JT, Saunders NR, Sharp F, Stanimirovic D, Watts RJ, Drewes LR. Engaging neuroscience to advance translational research in brain barrier biology. Nat. Rev. Neurosci. 2011;12:169–182.

[19] Maroon JC, Field M, Lovell M, Colins M, Bost J. The evaluation of athletes with cerebral concussion. Clin. Neurosurg. 2002;49:319-332.

[20] Hoge CW, Goldberg HM, Castro CA. Care of war veterans with mild traumatic brain injury. N. Engl. J. Med. 2009;360(16):1588-1591.

[21] Arundine M, Tymianski M. Molecular mechanisms of glutamate-dependent neurodegeneration in ischemia and traumatic brain injury. Cell Mol Life Sci. 2004;61:657-668.

[22] Blaylock RL, Maroon JC. Immunoexcitotoxicity as a central mechanism in chronic traumatic encephalopathy – a unifying hypothesis. Surg. Neurol. Int. 2011:2:107. doi: 10.4103/2152- 7806.83391.

[23] Zongo D, Ribéreau-Gayon R, Masson F, Laborey M, Contrand B, Salmi LR, Montaudon D, Beaudeux JL, Meurin A, Dousset V, Loiseau H, Lagarde E. S100-B as a screening tool for the early assessment of minor head injury. Ann. Emerg Med. 2012;59:209-218.

[24] Vincent A, Bien CG, Irani SR, Waters P. Autoantibodies associated with diseases of the CNS: new developments and future challenges. Lancet Neurol. 2011;10:759–772.

[25] Raabe A, Grohms C, Sorge O, Zimmerman M, Seifert V. S-100B protein in severe head in jury. Neurosurgery. 1999;45(3):477-483.

[26] Poletaev AB, Morozov SG, Gnedenko BB, Zlunikin VM, Korzhenevskey DA. Serum anti- S100b, anti-GFAP and anti-NGF autoantibodies of IgG class in healthy persons and patients with mental and neurological disorders. Autoimmun. 2000;32:33–38.

[27] Biberthaler P, Linsenmeier U, Pfeiffer KJ, Kroetz M, Mussack T, Kanz KG, Hoecherl EF, Jonas F, Marzi I, Leucht P, Jochum M, Mutschler W. Serum S-100B concentration provides additional information for the indication of computed tomography in patients after minor head injury: a prospective multicenter study. Lancet. 1995;346: 221-223.

[28] Maetzler W, Berg D, Synofzik M, Brockmann K, Godau J, Melms A, Gasser T, Hörnig S, Langkamp M. Autoantibodies against amyloid and glial-derived antigens are increased in serum and cerebrospinal fluid of Lewy body-associated dementias. J. Alzheimers Dis. 2011;26:171– 179.

[29] Gruden MA, Davidova TB, Malisauskas M, Sewell RD, Voskresenskaya NI, Wilhelm K, Elistratova EI, Sherstnev VV, Morozova-Roche LA. Differential neuroimmune markers to the onset of Alzheimer's disease neurodegeneration and dementia: autoantibodies to Abeta((25– 35)) oligomers, S100b and neurotransmitters. J. Neuroimmunol. 2007;186:181-192.

[30] Storace D, Cammarata S, Borghi R, Sanguineti R, Giliberto L, Piccini A, Pollero V, Novello C, Caltagirone C, Smith MA, Bossù P, Perry G, Odetti P, Tabaton M. Elevation of {beta}-amyloid 1-42 autoantibodies in the blood of amnestic patients with mild cognitive impairment. Arch. Neurol. 2010;67:867–872.

[31] Lehman EJ, Hein MJ, Baron SL, Gersic CM. Neurodegenerative causes of death among retired National Football League players. Neurol. 2010;79:1970-1974.

[32] Vincent A, Lang B, Kleopa KA. Autoimmune channelopathies and related neurological disorders. Neuron. 2006;52:123-138.

[33] Janigro D. Are you in or out? Leukocyte, ion, and neurotransmitter permeability across the epileptic blood-brain barrier. Epilepsia. 2012;53(Suppl 1):26-34, 2012.

[34] Ocwieja KE, Mihalik JP, Marshall SW, Schmidt JD, Trulock SC, Guskiewicz KM. The effect of play type and collision closing distance on head impact biomechanics. Ann. Biomed. Eng. 2012;40:90-96.