Suzanne Gazda MD, ISEAI

How Autoantibodies Circumvent the Blood-Brain Barrier (BBB) in Autoimmune Encephalitis"

First; we need to understand, what is the BBB?
Why does it start to breakdown and let 'stuff' in?

The blood-brain barrier is a filtration system, letting in good things (glucose, amino acids) and keeping out bad things (viruses, bacteria, toxins, metals, anything infectious for example). It's mostly comprised of endothelial cells lining the 400 miles of arteries, veins and capillaries that feed our brain and it provides the critical separation from blood and Central Nervous System (CNS). The BBB dysfunction can lead to ion dysregulation, altered signaling, deranged homeostasis, as well as the entry of immune cells and molecules into the CNS--processes that lead to neuronal dysfunction and degeneration.

The BBB[i] consists primarily of;
1. Endothelial cells (EC's) and tight junctions (TJ's) that connect them. The EC coordinate most of the metabolic and transport mechanisms. They are the building blocks of the BBB. The TJ's connect and help regulate movement of substances across the BBB.
2. Astrocyte foot process': these are so cool!! these create a protective sheath around the blood vessels. Remember that astrocytes provide most of the scaffolding or structure support in the brain.
3. Pericyte cell (PC's) are embedded in the vascular membrane. These cells contain *contractile proteins* and help control/contract the diameter of the capillary. They can be *pluripotent stem cells.*
4. Basement membranes.[ii]
BBB Diagram
BBB Images

How do we document damage to the BBB? While there are no readily available lab tests, other than the "investigational" (so managed care organizations & Medicare don't have to pay for it) S100B Calcium Protein Binding Protein the only way to really look at damage to the BBB is indirectly; looking at effects of what the damage is doing

The BBB gets 'leaky' for a lot of reasons; the biggest reasons are:
1. Cytokines produced in response to inflammation (from gut, infections, toxins, chemicals, etc.).
2. Auto-antibodies produced in the periphery (like with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), Multiple Sclerosis (MS), Lupus, etc.).
3. What is most fascinating (to me) is the route of inflammation that begins in the olfactory system (no wonder mold is such a bad actor, i.e. it is not only lipophilic and therefore easily gets thru the BBB delivering intense neuroinflammation and that sneaks in thru the olfactory sensory neurons to the olfactory bulb adjacent to the thalamus (router of the brain) & hypothalamus-pituitary which is where the brain/endocrine-hormone system connects.

Once this process starts, it is hard for the brain to correct the problem unless WE jump in and help.

If we are going to "repair ' the BBB, then we must work hard to find all the factors fueling the destruction of this incredible line of defense in the CNS.

I really don't think getting a test for BBB dysfunction is necessary at all, for, if you have neurological signs & symptoms (especially anything autoimmune like MS, Guillain-Barre, or anything 'neurodegenerative '). We have to assume that the BBB has been broken down. I believe this applies even to people with headaches, facial pain, peripheral neuropathies etc. We can *see all of this on* the NeuroQuant studies.

The Experimental Autoimmune Encephalomyelitis (EAE) model has taught us so much not just about MS but about CNS neuro-inflammation/immune attack in the brain. Attached[iii] is a study that looked at gut dysfunction and MS, and when zonulin was elevated. The patients had more CNS activity on MRI. Once this immune dysfunction gets going in the brain, more and more breakdown of the BBB occurs. We really should all be focused on BBB recovery in every patient with neurological problems

It is clear that there is BBB dysfunction in many different neurological diseases in a wide variety of species, thus, this is an evolutionarily conserved important feature of these diseases. This makes sense from an evolutionary perspective—to protect the organism from brain damage from infection, toxins or other sources. A critical question moving forward is to understand which aspects of this BBB dysfunction are healing and which aspects are pathological. Like any inflammatory event, a small amount is likely helpful in clearing debris, fighting pathogens, and aiding in wound healing, whereas a large amount can cause debilitating causing tissue dysfunction and degeneration.

Basically, there is no one way this happens, it is complex--so there is no simple solution to fixing the problem.

But there are some things that will help:

1. Turn off the Cell Danger Response (CDR) and reduce inflammation.
2. Upregulate Mitochondrial function and up regulate autophagy (the process by which damaged cells, intercellular debris and “garbage” byproducts of metabolism are “eaten” by macrophages and removed from the system).
    a. The BBB (especially the endothelial cells and astrocytes that line the BBB are RICH in mitochondrial function).
    b. Many believe that mitochondrial function lies behind most disease/pathology states we know for sure mitochondrial function is at the heart of all CNS (and many other sources of) pathology/disease states.
3. Aging, Autoimmune disease, Cancer, Neurodegenerative disease etc.
    a. Astrocytes and microglia control CNS inflammation and neurodegeneration--both are highly rich in mitochondria
4. Heal the gut: The Gut Brain cross-talk is huge.

    a. Gut microbes may affect the host by reprograming immune cells, promoting cytokine secretion, manufacturing bacteriophages, all moving into the systemic circulation and in many cases crossing the BBB[iv]
5. Diet: Anti-inflammatory is a must.
    a. Consider ketogenic/intermittent or more prolonged fasting to induce autophagy
6. Sleep: The BBB needs some help and sleep is so important.
    a. Blood-brain barrier transport and glymphatic clearance likely serve complementary roles. (Neurosci Biobehav Rev. 2018 Jul;90:26-33. doi: 10.1016/j.neubiorev.2018.03.028. Epub 2018 Mar 30)

There are many, many more things we can do to 'heal the brain'!

---

[i] The Blood–Brain Barrier https://mail.google.com/mail/u/2/#inbox/FMfcgxwDqxJhGxggwGGrzTdPZTNbplSC?projector=1&messagePartId=0.5

[ii] BBB Image https://drive.google.com/file/d/1YZlZIiyEEaCr3yw-R7LW2-4PqwsKrm_k/view?usp=sharing

[iii] Hello from the Other Side: How Autoantibodies Circumvent the Blood–Brain Barrier in Autoimmune Encephalitis https://mail.google.com/mail/u/2/#inbox/FMfcgxwDqxJhGxggwGGrzTdPZTNbplSC?projector=1&messagePartId=0.3

[iv] Biomarkers of intestinal barrier function in multiple sclerosis are associated with disease activity. https://mail.google.com/mail/u/2/#inbox/FMfcgxwDqxJhGxggwGGrzTdPZTNbplSC?projector=1&messagePartId=0.4