Title: The Brain on Fire – The Role of the damaged Blood Brain Barrier and Neuro-inflammation in Neurological Disorders and Chronic illness

Reference:

Lopez-Ramirez, M. A., Wu, D., Pryce, G., Simpson, J. E., et.al. MicroRNA-155 negatively affects blood–brain barrier function during neuroinflammation. FASEB J. 28, 2551–2565 (2014).

Clinical Discussion:

Before discussing the mechanics and relativity of this data to neurological symptoms I would like to describe the process I will use in this review: What is it? How does it work and cause disease? What else do we know about this? And most importantly: What can we do about it? I say this as the topic sounds so microscopic and arcane in nature, but as always what we will see is that natural medicine can profoundly impact this emerging cause of human pathology and suffering.

A question I am often asked is ***"what does this actually look like when it happens to a patient?"*** The answer is that anything the brain does for the body can be impacted by this inflammation and become abnormal and symptomatic. I have seen most commonly aggravation of primary neuro-emotional states such as depression, anxiety, sleep disturbance, agitation and the like. Additionally (and quite disturbing to the patient as well as practitioners unaware of the phenomenon) I have seen what appeared at first to be stroke like symptoms, memory loss, migraine like symptoms and even altered perceptions of reality occur when the nervous system becomes inflamed.

The next question is ***"can you test for it and can it be treated?"*** I began reporting these symptoms in infectious disease patients in the 1990's and at the time little was considered about the phenomenon in North America. About 15 years ago I attended a conference where a German physician was speaking about the link between the GI barrier breakdown, infections and autoimmunity and a resultant breakdown in the blood brain barrier and central nervous system inflammation. This description matched my case reports and I began research into the mechanisms, testing and therapy. There are tests specific for the nervous system break down but they are really only used in neuro-research labs. Other more global tests such as CRP, LDH and others are often falsely negative. Neuro imaging can help but again is typically not needed if the signs and symptoms are followed. Treatment is often slow but necessary to keep the inflammatory response under control. Below are some brief pointers to symptom picture keynotes and therapeutic strategies.

Symptom picture:

- Aggravation or accentuation of a known neuro-emotional state (anxiety, depression, agitation, sleep disorder, OCD etc.)
- Rapid new onset of any of the above or any related neuro-emotional state.
- Altered perceptions of reality (paranoia, feeling like someone else, feeling out of place, "Déjà vu" experiences etc.)
- Signs and symptoms normally associated with migraine, TIA, stroke etc. (See the note below, but I have seen people with this phenomenon have hemiplegia which resolved totally during an anti-inflammatory IV (and who had completely normal brain MRI later the same day).

Note: I have seen all of the above in cases that became neuro-inflammatory, and they always resolved with treatment. Of course screen every patient with stroke or other signs with an extensive clinical history, neurological examination and imaging if needed. A note on imaging in these cases: I used imaging in the days before we knew what was happening and never saw any pathology. This led me to investigate the phenomenon written about here "what can act like a stroke or acute psychosis but not be that diagnosis?" - It is why I so strongly suggest a very good history and physical exam along with watching for quick onset and resolution while weighing imaging as an option.

Therapeutic ideas:

- Manage the primary triggers which normally are infections and autoimmune pathology, toxicity, inefficient thyroid and adrenal support, low neurosteroid levels and others.
    - Aggressively increase needed support in these areas especially Adrenal and Neurosteroid agents.
    - Also consider alterations in infections, biofilm, toxicity and other therapies.
- Increase the calming agents (see below as well) for the inflamed nervous system during a flare, and if possible use IV route as a loading dose.
- Monitor and reassure the patient. It is very frightening for them and a time when the case must be followed closely.

What is MicroRNA and how can it be so impactful in pathologies?

From the Abstract: "Blood–brain barrier (BBB) dysfunction is a hallmark of neurological conditions such as multiple sclerosis (MS) and stroke. However, the molecular mechanisms underlying neurovascular dysfunction during BBB breakdown remain elusive. MicroRNAs (miRNAs) have recently emerged as key regulators of pathogenic responses, although their role in central nervous system (CNS) microvascular disorders is largely unknown. We have identified miR-155 as a critical miRNA in neuro-inflammation at the BBB. miR-155 is expressed at the neurovascular unit of individuals with MS and of mice with experimental autoimmune encephalomyelitis (EAE)." I have reviewed other papers in the past few years which focus a lot of the weight of pathologic triggering in neuro-inflammatory disorders on the inflamed and incompetent BBB. This lack of control due to BBB inflammation leads to a host of disorders including neurological autoimmunity, psycho-emotional disorders, infectious diseases and even depression. So the more we understand about the genesis of the inflamed or "leaky" BBB the more we can target its healing. The elucidation of the implication of microRNA activity in CNS and BBB dysfunction is yet another step in knowing exactly the cause we are supposed to treat.

What else do we know about miRNAs / miR-155?

In addition to inflammation and dysfunction of the BBB and CNS, miR-155 is known to be implicated globally in multiple immune system regulatory processes. The activity of miR-155, and miRNAs in general crosses over multiple immunological parameters including cancer control or stimulation [1,2] and infectious disease [3] as well as generally providing counter regulation over the immune system.

MicroRNAs are considered "non-coding" RNA which formerly were of unknown significance and even occasionally categorized as "junk" in the genome. Although miRNAs are the most studied non-coding RNAs (ncRNAs) to date, the importance of long non-coding RNAs (lncRNAs) is increasingly being recognized and are showing themselves to be a deep well of potential in actual cell to cell regulatory function.

Examples form oncogenesis include the following: Inactivation of mismatch repair (MMR) is the "cause of the common cancer predisposition disorder Lynch syndrome (LS), also known as hereditary nonpolyposis colorectal cancer (HNPCC), as well as 10– 40% of sporadic colorectal, endometrial, ovarian, gastric, and urothelial cancers. Elevated mutation rates (mutator phenotype), including simple repeat instability [microsatellite instability (MSI)] are a signature of MMR defects. MicroRNAs (miRs) have been implicated in the control of critical cellular pathways involved in development and cancer." [1]

Overexpression of miR-155 significantly down-regulate core MMR proteins, inducing a mutator phenotype and MSI. This is a mechanism of miR-155 modulation of MMR as a mechanism of cancer pathogenesis.

In infectious disease one highly studied pathogen, Mycobacteria, have been used to map out part of the effect MicroRNA have on immune function. "microRNA-155 (miR-155) plays an essential role in regulating the host immune response by post-transcriptionally repressing the expression of target genes. However, little is known regarding its activity in modulating autophagy, an important host defense mechanism against intracellular bacterial infection. Mycobacterial infection triggers the expression of miR-155, and the induction of miR-155 in turn activates autophagy by targeting Rheb, a negative regulator of autophagy. miR-155-promoted autophagy accelerates the maturation of the mycobacterial phagosome, thus decreasing the survival of intracellular mycobacteria in macrophages."[3]

As these few papers show the activity of MicroRNA and miR-155 specifically have far reaching effect in many aspects of immune function.

How can we use this data to improve or enhance clinical interventions in integrative medicine?

I do get accused of "geeking out" over immunology, cytokine activity and all manner of minutia in medicine and that of course is true. It is certainly cool to know information like this but the crucial factor is ***what does this add to our knowledge and ability to effectively help people?*** This is an example of essentially one more data set (yes, delving deeply into immunology) providing evidence that natural therapies can affect the human system very deeply in either keeping or moving back toward balance and health promoting chemistry and communication. We have seen that many natural products for example can help rebalance TH-1/TH-2/TH-17 and other factors as an example. The use of natural agents to help keep normal function in and restore normal function to miR-155 (thereby causing more robust health and immune function) is also studied. A summary below of known effectors of miR-155 follows. The major take home message to me is that in cases of CNS/BBB dysfunction, infectious illness and cancer caring for the miR-155 portion of the immune system is crucial and can be aided with traditional natural products.

Therapies studied:

General nutritional cell regulators such as Vitamin D, Folate, Indoles, Polyphenols, Retinoids and the like are shown to promote balanced function of miR-155. [5]

Herbal medicines used the world over (although some are more common in Asia) which have been studied include Berberine, Curcumin, Camptothecin, Resveratrol, Ginsenoside, Luteolin, Isoflavones, Matrine, Aidi Injection, Ganoderma, Coptidisrhizoma, Mistletoe lectin-I and Honokiol. [4]

Specific Chinese formulas including Hedyotis diffusa plus Scutellaria barbata have been studied in miR-155 activity in bladder cancers as well. [6]

When one reads the list above it is of course a "who's who" of mostly common natural therapies used in immune conditions including CNS inflammation and cancer. Some surprised me from the point of view of their being very common traditional naturopathic and or Asian medicine treatments – but then the surprise was not that they would work but that there are yet more scientific data supporting what we have done for centuries. This paper gave me a wonderful insight into additional ways to heal CNS/BBB dysfunction which is ubiquitous in the chronic disease patient population. In looking for the supporting references it led to many happy surprises in correlating those therapies with improving immune function in cancer and chronic infections.

References:

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