TBI Therapy
Regenerative Therapy for Brain Injury

TBI Therapy Modalities: Principles and Practice

Nasal Specific (aka Craniofacial Release)

Overview

"Nasal Specific/Bilateral Nasal Specific (BNS) is a controlled approach and technique that works to unwind the body and help it return to a more optimum function by adjusting the cranial plates of the skull and re-leaving pinned up pressure that affects the nervous system and re-establishes the flow of cerebrospinal fluid to the body and the proper flow of blood to the brain….

A finger cot/balloon is slid into the nasal passageway the patient is asked to breath out through their nose, this allows access and proper placement of the balloon into the passageway. The balloon is gently tucked in around the outer edges of the nostril with a flat toothpick to ensure that no outward bulging of the balloon occurs when it is inflated. The nose is lightly compressed around the valve of the pressure bulb, so that no air can escape. The patient then takes a deep breath in and holds it….

When the pressure bulb is pumped it causes the finger cot/balloon to expand inside the nasal passageway. This expansion pushes against the compressed walls clearing out accumulated mucus and pushes its way through the nasal passageway into the upper back portion of the throat, where the balloon taps against the tissue that is directly in front of the sphenoid bone. By taping on this area it also taps the sphenoid causing it to shift ever so slightly. This shifting causes the other cranial plates to shift/realign and at that moment it releases built up pressure that is housed in the joints/membranes, inside of the skull. It releases pressure that has puts adverse impact on the brain, and also allows the pinched cerebrospinal fluid tubes and the blood vessels to be released so that optimum function is restored, it also restores proper respiratory breathing patterns, restores normal sinus drainage, stimulates the Pituitary Gland, stimulates and unlocks the Vomer bone so that it can articulate properly.[1]"

Application for TBI Treatment

At TBI Therapy, we began using Nasal Specific primarily to open up the nasal cavity to improve insertion of the catheter into the upper nares. Nasal Specific was, in the mind of Dr. Hughes, simply a means to an end--of providing intranasal plasma to the brain through the cribriform

[1] http://www.nasalspecific.com/nasalspecific_002.htm [accessed online 1-1-2017]

fossa and associated nerve channels. However, upon hearing the multiple patient reports after getting just one or two Nasal Specific treatments, the benefits of the therapy were evident. The most common reports include better ability to breathe, more symmetrical skull and facial bones, clearer thinking, more stable moods, and better memory.

These reports are consistent with those made by other practitioners: "The side effects most commonly noted include ability to clearly breath, do to the fact that it clears out the sinuses, increased energy, due to stimulation to the nervous system, and breathing capabilities, sharper memory, increased sensation of joy or happiness, and facial proportion balance. It also increases the ability to function better and aids in lessening of a wide array of dysfunctions and disabilities."[2]

For patients with a TBI, which frequently involve skull fractures, Nasal Specific works to resolve the compressive cranial deformations that often occur with brain injuries...from the inside out. The skull, including the facial bones, fits together like pieces of puzzle--a puzzle with dynamic interfaces. With internal pressure on these cranial and facial sutures, the puzzle has the opportunity to reset itself in its proper most fluid state.

The proper connections of cranial sutures will determine how the blood, CSF, lymph, and nerves flow underneath the skull, around the brain and even down the spinal column. Stagnation in the flow any of these blood, CSF, lymphatic, or nerve channels due to compressive injuries can lead to head pressure, headaches, memory loss, vision disturbances, hormone disorders, paralysis, mood changes, or a variety of the other post-concussive symptoms experienced by TBI patients. Combined with skilled cranial osteopathy, Nasal Specific can improve the overall oxygenation, nourishment, detoxification, and innervation of the brain by removing the restrictions affecting overall flow to the brain.[3]

Put simply, if you were to grossly fix the dent in your car's body, it would be most effective to push out on the indentation from the inside outwards. Nasal Specific techniques do just that for the human skull.

Protocol

The effective dosing of Nasal Specific is 5 initial treatments for most patients. For patients travelling into town for only 3 days, 1-2 NS treatments will suffice. For patients staying for the 10 protocol, an ideal NS treatment is 1-2x/week for a maximum of 4 treatments. For patients staying for the 40 day treatment, 1 NS treatment per week is fine. Patients with a more severe TBI may require less aggressive protocols.

Safety/Side Effects

While most patients applaud the benefits of Nasal Specific, some patients do suffer from a few side effects. One of Dr. Hughes' patients experienced some bruising above the right eye, where she had suffered from an orbital fracture. Otherwise, the side effects are as described: "The

[2] http://www.nasalspecific.com/nasalspecific_003.htm

[3] See more about the science of CSF and blood flow in the "Cranial Osteopathy" discussion.

side effects include sore gums, sore upper throat and a temporary feeling of being exhausted, due to the release of stored negative energy. At times there may be a bit of light bleeding due to the finger cot/balloon pressing up against the compressed walls of the nasal passageway."[4]

This is pretty good film link by Cynthia Stein PT MEd from group called Conquer Concussion:

https://www.youtube.com/watch?annotation_id=annotation_2401096303&feature=iv&src_vid=hQcZT3l7my8&v=ihHSst8DzQg

Cranial Osteopathy

Overview

Cranial osteopathy (aka Cranial Therapy or Cranial-Sacral Therapy) is based on the fact that the central nervous system, including the brain and spinal cord, has subtle, rhythmic pulsations that are vital to health and can be detected and modified by a skilled practitioner.

"Osteopathy in the Cranial Field has gained a special position within the many dimensions of osteopathic medicine. The underlying causes of severe pathological disturbances are to be found in cerebrovascular insufficiency and impaired cerebrospinal fluid circulation. Throughout the early development of osteopathic medicine, Dr. Andrew Taylor Still, its founder, paid special attention to the cerebrovascular and cerebrospinal systems. The role of these systems was well known to him at the end of the XIX Century. He appreciated their respective dominance in body physiology. Another enlightened pioneer, Dr. William G. Sutherland, who advanced osteopathy into the cranial field, recognized the significance of slow fluctuations arising within the cranium, which could be responsible for skull bone motion."[5]

Dr. Sutherland defined this motion as the Primary Respiratory Mechanism in the 1930s…."The PRM according to Sutherland includes a number of structural or anatomical elements namely brain, blood vessels, meninges, the cranial bones with their delicate articular design of sutures and the reciprocal tension membrane of dura mater. Within the cranium there is the source of the special physical forces, which initiate the cranial rhythmic impulse and skull bone motion."[6]

"Experimental and clinical observations demonstrate that relations between main parameters specific for CV (cerebrovascular) and CSF (cerebral spinal fluid) systems are complex….
For example, in one combination of primary factors, if arterial volume increases, cerebral blood flow (CBF) increases together with increase of intracranial pressure (ICP), but if venous volume

[4] http://www.nasalspecific.com/nasalspecific_003.htm
[5] Moskalenko, Y., Frymann, V., Kravchenko, T., & Weinstein, G. (2003). Physiological Background of the Cranial Rhythmic Impulse and The Primary Respiratory Mechanism. The AAO Journal, 2003, V.13, No.2, P.21-33
[6] Ibid

inside the cranium increases or outflow of CSF to spinal cavity is obstructed, increase of ICP will be accompanied by a decrease of CBF."[7]

Hence, osteopathic manual therapy to skull bones that encourages appropriate, balanced CSF flow (assessed through the cranial rhythmic impulse at 8-12 cycles/min) allows for the proper CBF (arterial and venous), normal ICP, and overall oxygenation and nourishment of the brain.

Application for TBI

Regional brain blood supply is determined not only by hemodynamic factors but also by CSF mobility. Therefore, if resistivity of CSF pathways increases, the regional CBF will decrease, and this may be the explanation of some kinds of neurological deficit. Such a situation might be one of the consequences of brain injury. In this case the appropriate osteopathic techniques could increase the CSF circulation in the injured brain region.

Numerous experiments have determined that "slow fluctuation of cerebral blood flow closely correlate with local fluctuations of brain blood volume and oxygen availability in brain tissue." Recent applications of spectral analysis have shown (Moskalenko 2000, Moskalenko et at 2001) that slow fluctuations are composed of extracranial fluctuations of arterial pressure and respiratory chest movements, and of intracranial fluctuations namely redistribution of CSF volumes inside skull.

One key experiment has been to measure how CSF and CV flow during a single cardiac cycle using 2 different parameters. The most acceptable test is a "combination of simultaneous recordings of Bio-Impedance (B-Imp) and transcranial dopplerography (TCD), because these methods are based on different physical principles and, therefore, reflect different aspects of the functioning of CV and CSF systems. Indeed, B-Imp records the change of electrical conductivity between plate electrodes, placed on the human head, for high frequency (50-70 kHz) electrical current. Because electrical conductivity of blood and CSF are different (for blood it is about half that for CSF), their comparative volume changes will change the electrical conductivity between electrodes."[8]

The following figure compares the CSF flow (represented by t) of a healthy person, an athlete, and a TBI patient. It was found that "t", translated as "CSF mobility" was greatest in the athlete, normal in the healthy person, and significantly smaller in the TBI patient. In very simplistic terms, if we think of the CSF as a abundant river of fluid circulating the brain and spinal column, that river is stagnant and restricted in the TBI patient. See Figure 5 below.

[7] Ibid.
[8] Ibid.

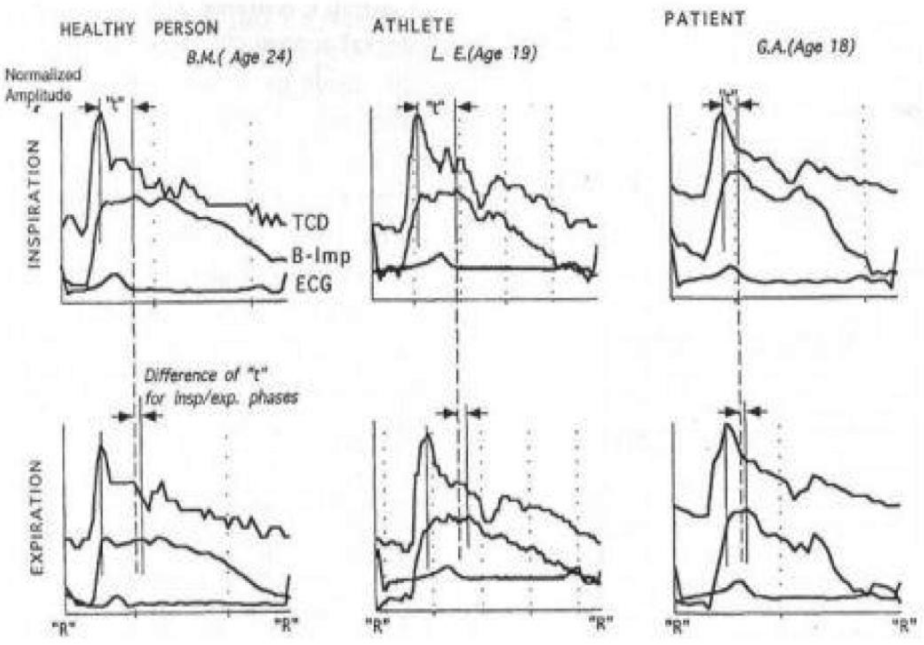


Figure 5: The difference of "t" between inspiratory and expiratory phases of the secondary respiration in a Healthy person, Athlete trained in diving and Patient after head injury.

Time shift between peaks of TCD and B-Imp is determined by the replacement of some portion of CSF out from (or into) zone of B-Imp electrodes. Thus this time interval represents the mobility of CSF inside the cranium during the pulse cycle. At this period no active processes could operate. Investigations under different conditions have shown that "t" reflects CSF mobility.

In sum, CSF motility (along with CV flow), can be assessed and addressed by the osteopathic practitioner via the CRI. The CRI can be felt as the subtle motion of the skull bones. Encouraging an improved CRI by the cranial osteopathic practitioner is a significant way to positively affect the primary respiratory mechanism and overall metabolic and neurovascular health of the brain.

Protocol

For TBI patients, it is key to gauge the therapy per the patient. Ideally, a patient should get no more than one 30-60 minute cranial session per week. “Touch up” cranial therapy treatments may be done for 15-20 minutes that same week or done after another associated procedure, such as nasal specific or intranasal PRP.

Safety/Side Effects

Cranial osteopathy, while a subtle therapy, is not be taken lightly. Due to the increasing popularity of massage and other manual therapies, it is very easy for a lay practitioner to learn a

few cranial techniques that manipulate the skull but fail to acknowledge the key purpose of syncing these techniques with the CRI as well as the limits of each patient. Hence, while cranial osteopathy, if done poorly, has only a benign, transient effect on the patient, it may be that the patient experiences increased head pressure, headache pain, or emotional distress due to the therapy. All practitioners, whether trained as osteopathic physicians or not, must work to be careful with the treatment, always assessing the CRI as his or her guide for more or less therapy to any particular area of the skull.

This is a pretty good film by osteopath Tony Bryant.

https://www.youtube.com/watch?v=lPB9LfYqFMc

Also see http://tbitherapy.com/tbi-protocol-references/

Hyperbaric Oxygen Therapy

Overview

Hyperbaric oxygen therapy has been a mainstay treatment for severe conditions such as non-healing skin ulcers, carbon monoxide poisoning, decompression sickness, and as an off-label treatment for TBI for the past few decades. Almost every major hospital is equipped with these rather large compression medical grade chambers that can take patients to depths of 3 atmospheres or more.

Application for TBI

The science behind hyperbaric for TBI patients is vast.[9] It has been shown that breathing 100% oxygen at increased atmospheric pressures allows the body to absorb about 10-15 times its normal supply of oxygen. This “high dose” oxygen, stimulates the growth of neuronal tissue, bone and blood vessels, reduces inflammation, and mobilizes stem cells.

Two hours of HBOT at 2 ATA doubles the patient’s own circulating stem cells; 40 hours of HBOT at 1.5-2.0 ATA increases circulating stem cells to 8 fold (800%). This stem cell increase results from an increase in nitric oxide in the bone marrow. Nitric oxide stimulates enzymes that mediate stem/progenitor cell release.

The benefits of hyperbaric oxygen therapy on CBF can be seen in the following nuclear spect scan.[10]

[9] http://tbitherapy.com/tbi-protocol-references/

[10] Boussi-Gross, R., Golan, H., Fishlev, G., Bechor, Y., Volkov, O., et al. (2013) Hyperbaric Oxygen Therapy Can Improve Post Concussion Syndrome Years after Mild Traumatic Brain Injury – Randomized Prospective Trial. *PLoS ONE 8*(11): e79995. doi: 10.1371/journal.pone.0079995.

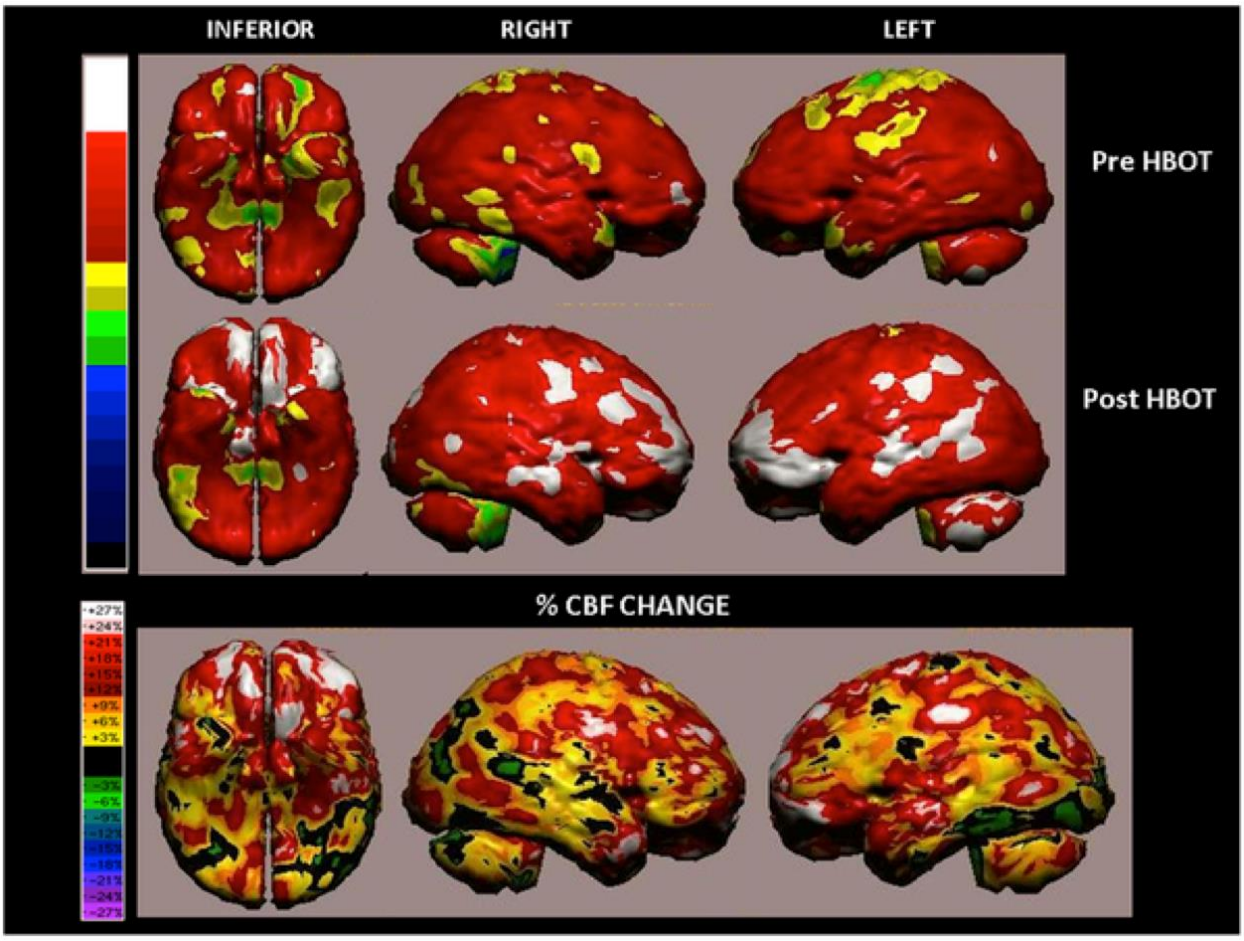


Figure 1. Volume rendered Brain SPECT perfusion maps of Example 1, a 51-year-old woman from the treated group suffering mTBI that had occurred 2 years prior to inclusion in the study.

While reduction of inflammation, tissue growth, angiogenesis are all important aspects of HBOT's beneficial effects for TBI patients, the stem cell release has been the particular focus of Dr. Hughes at TBI Therapy. In the U.S., stem cell clinics do not have the privilege, per FDA regulations, to "grow up," culture autologous human stem cell outside the body for 3 weeks as is allowed in more stem cell friendly countries. For stem cell practitioners, HBOT solves this issue by allowing the body to upregulate and send stem cells to the most needed areas of healing. This stem cell upregulation fact has been seen clinically with one of Dr. Hughes' patients, Mr. Chad, who has used both medical grade and home HBOT chambers extensively since his TBI in August 2012. In March 2015, Dr. Michael Brown, MD performed a procedure to harvest autologous platelet derived cells from Mr. Chad and found that he had 3.5 billion cells per mL of plasma collected. Dr. Brown and his colleagues thought the cell counter machine was incorrect because Mr. Chad's cell counts were over 23x the average patient's counts~normally 150 million cells. 23X!

See http://tbitherapy.com/tbi-protocol-references/ for more scientific journals supporting the use of HBOT for TBI.

Protocols

In the past several decades, Dr. Paul Harch, MD has helped to further develop and standardize the protocols for HBOT's use for the treatment of TBI. The primary protocol has been to treat the TBI patient (mild, moderate, severe) with the same 40 treatment protocol at 1.5 ATA for 1 hour at depth. Nonmedical home chambers have been scorned and discounted as having any value. This one-size fits all approach has been adopted and utilized by HBOT clinics around the US, which positive success for the patients treated, but limited by the scope of patients that can devote the time (6-8 weeks) and financial resources ($5000-8000) to commit to this protocol. And, in fact, HBOT alone, even over 40 treatments, may not resolve the long-term post concussion sequela experienced by TBI patients. Finally, most insurance plans and government organizations balk at the idea of paying for this type of long-term therapy for TBI patients. This battle between science and the business of treating TBI by medical insurers and other third parties has led to a stalemate and ultimately, the a failure for any practitioners to incorporate even shorter bursts of HBOT or home HBOT chambers into their treatment of TBI.

At TBI Therapy, we have sought to change the fundamentalist protocol of 40 HBOT treatments for all but the most severe TBI patients. We allow the patients to utilize their own home HBOT chambers at 1.3-1.4 ATA before coming to get medical HBOT treatments at 1.5-2.0 ATA. Dr. Hughes has developed 3-10 day programs for patients with their own chambers (or milder brain injuries or who have already completed 40 HBOT treatments) that incorporate all of the discussed modalities of therapy including HBOT, cranial osteopathy, nasal specific, intranasal therapies, ketogenic nutrition, IV nutrition, and binaural rhythms. Every patient who utilizes this mult-modal TBI Therapy treatment gains some form of benefit, even with just a small number of HBOT sessions. Patients report sleeping well, having more mental energy, more clarity, more physical energy, and improved memories.

It is theorized that multi-modal therapy for TBI (including antioxidant IV nutrition and IN glutathione) also allows patients to sustain deeper dives beyond 1.5 ATA. Part of the rationale for keeping patients at 1.5 ATA is the fact that the patients may suffer from more oxidative stress with higher pressures. As one would do with a athlete, using appropriate nutrition can protect against this oxidative stress and improve the overall benefit of HBOT therapies for the TBI patient.

Also, thinking of HBOT as akin to athletic training for the brain injured patient, it has been found that "altobaric training" may be more effective than monobaric training. Altobaric training means that the patient is not simply kept at 1.5 ATA (or any consistent pressure) for more than a short amount of time (10 minutes or less) so that the body and brain have to adapt to changing pressures. This is kind of like interval training for an athlete. A typical altobaric HBOT protocol might include spending 10 minutes at each depth: 1.4, 1.6, 1.8, 2.0, 1.8, 1.6, 1.4 ATA over a 1.25 hour session. Some studies suggest a continued variation in pressure.[11]

Other protocols and adaptations include hypoxic training before going into the HBOT chamber.

[11] https://www.ncbi.nlm.nih.gov/pubmed/11434218

Dr. Adam Breiner reports that he has patients exercise on a bicycle for 15 minutes before getting into the chamber using a mask that makes the patient breathe air with less oxygen.[12] Dr. Hughes reports that simply having the TBI patient hold his or her breath for a minute while in the chamber is effective. Even elevating the lower extremities to improve CBF to the brain can be an effective way to help some patients.

Dangers/Side Effects

The biggest, most obvious danger of HBOT is the fact of being in an oxygen saturated environment. It is key for patients to remove all clothing that may create a spark, all jewelry, all perfumes, hair sprays, and all lotions. 100% cotton is the only clothing acceptable in medical grade chambers, provided most often as scrubs. Other not-so-obvious precautions include patients with sinus issues, claustrophobia, dental work, pulmonary fibrosis, or cardiac anomalies. TBI patients with V-P shunts are usually okay as long as the shunt is working correctly.

Dr. Hughes has seen sinus issues, barotrauma, and agitation as the biggest side-effects of treatment. Most TBI patients do quite well and enjoy the HBOT dives. Having an excellent technician is an absolute. Kirk Hartley from the Colorado Center for Hyperbaric Medicine is one of the best. Check out this film below and his website.

https://youtu.be/m0pjXLbTRQ4

http://www.cohyperbarics.com/

This is also a great lecture from Dr. Paul Harch, MD

https://www.youtube.com/watch?v=-cIYt6lBw_M

Intranasal Therapies

Dr. Hughes learned of intranasal treatments several years ago in 2009 from a friend of his father, Dr. T.R. Shantha, MD. Dr. Shantha had studied intranasal insulin as well as insulin potentiation therapy extensively. In 2013, a patient known as Mr. Chad, with a severe TBI, asked Dr. Hughes if he could do anything else for him instead of just authorize HBOT treatments. Mr. Chad lived in a dark warehouse and daily wore noise cancelling earphones in order to cope his noise and light sensitivity. He felt overwhelmed frequently and was unable to cope with stressors of work or social life. His memory was challenged.

Dr. Hughes told Mr. Chad about using intranasal insulin and also offered to use Mr. Chad's plasma as a carrier for the insulin. It was a rough process and Mr. Chad swallowed some of the mixture. The intranasal treatment was repeated on a second day. The results are best

[12] Hypoxico is a great resource for getting a hypoxic chamber or mask to help patients gain the maximum benefit of HBOT. http://www.hypoxico.com/ Note: TBI patients may only be able to handle a certain amount of hypoxic stress so gauge your treatments accordingly.

described in Mr. Chad's words:

"I was so hypersensitive to light and sound that I had to wear ear plugs, headphones, sunglasses, giant sun hat, and a scarf just to attend the appointment. I could not drive, I lived in darkness, and struggled emotionally. Dr. Hughes' demeanor was filled with humor, hope, and confidence. Since hope had pretty much gone out the window, it was refreshing to learn about new therapies. After the PRP treatment, it was like a stream of information had been let loose like a dam that had busted. I saw clips of memories such as faces, numbers, and letters. I felt for the first time in a year that I had some clarity. I was excited and able to read more than 2-3 sentences without triggering a migraine. I found that I was able to get back on the computer and learn more about my trauma and recent treatments. Within the following days, it was like an awakening. I could turn on lights for a few minutes and keep the TV on. It seemed like a light switch was turned back on inside my head. The ability to think and plan returned."[13]

At the time, Mr. Chad had also just completed 25 treatments of HBOT so Dr. Hughes felt that his progress may have been incidental to the increased oxygenation and blood flow he was experiencing as much benefit from the HBOT as much as the intranasal therapies. However, due to the almost instantaneous benefits that occurred within a few days, more research was put into the process of best delivering insulin, plasma, and nutrients to the brain intranasally.

There is a vast quantity of research regarding intranasal insulin and the study of Alzheimer's disease. Dr. Hughes contacted Dr. William Frey, one of the leading researchers in the discovery of using intranasal insulin in the late 1980's. Dr. Frey shared openly about his publications and the protocols associated with treating Alzheimer's disease with insulin. Dr. Frey also sent a study that discussed the use of insulin for TBI. The sum of insulin's effects on the brain include the following:

•improves brain ATP production

•decreases CSF cortisol

•improves neuronal viability in the hippocampus

•increases the expression of anti-inflammatory microglia

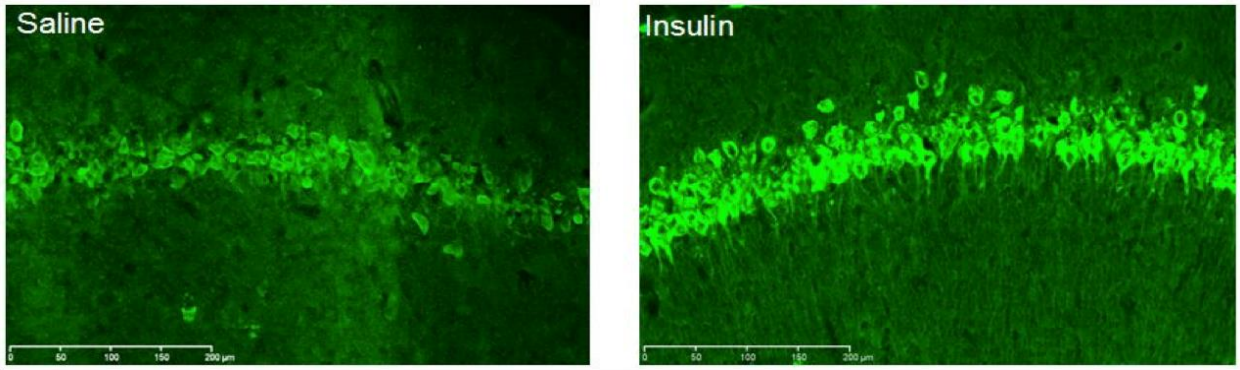
•reduces beta-amyloid and tau protein deposition

Intranasal (IN) insulin has extraordinary effects on the brain, now visualized and proven. See below figures for the effects on the neurons of the hippocampus and the microglia.[14]

Figure 2. NeuN staining was increased with intranasal insulin treatment

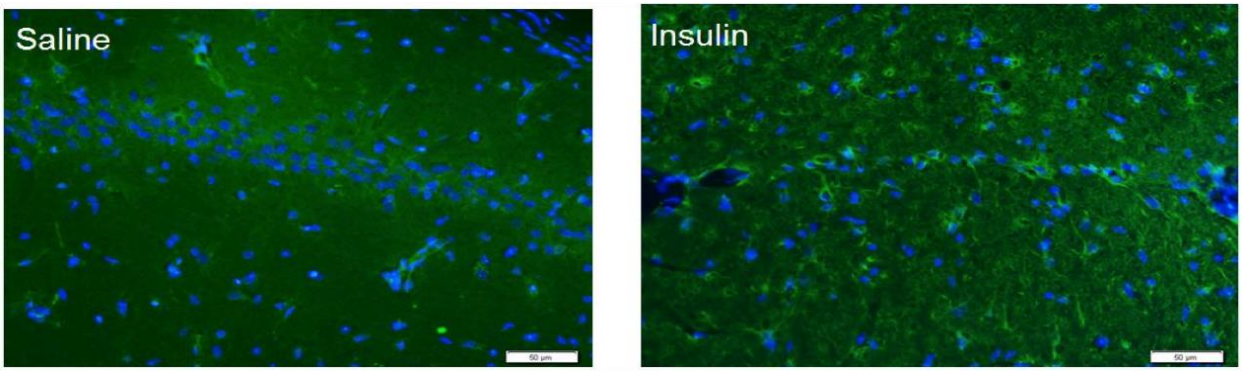
[13] http://tbitherapy.com/testimonials/

[14] Brabazon, F. P., Khayrullina, G. I., Frey, W. H., & Byrnes, K. R. (2014, June). INTRANASAL INSULIN TREATMENT OF TRAUMATIC BRAIN INJURY. *In JOURNAL OF NEUROTRAUMA (Vol. 31*, No. 12, pp. A106-A106). 140 HUGUENOT STREET, 3RD FL, NEW ROCHELLE, NY 10801 USA: MARY ANN LIEBERT, INC.



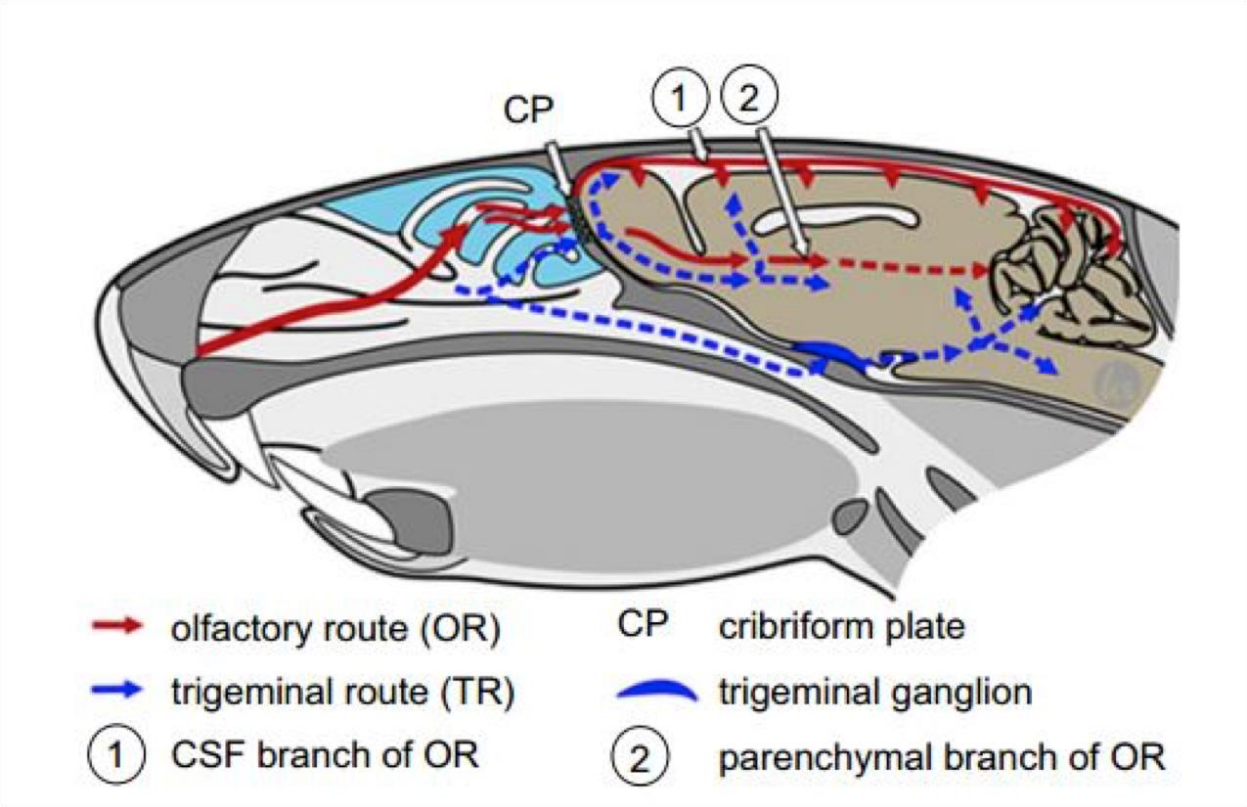
TBI results in neuronal cell death. Neuronal cell death in the hippocampus impairs memory function. NeuN, an immunohistochemical marker of neurons, was used to examine the effect of intranasal insulin on neurons after injury. Qualitative assessment of histology showed improved neuronal viability in the hippocampus of the insulin treated rats.

Figure 3. Intranasal Insulin increases the expression of anti-inflammatory microglia in the hippocampus



So how does the insulin, or any other nutrient, plasma, or drug get into the brain. It is theorized and most likely that the insulin and other substances bypass the blood brain barrier by traveling along the olfactory nerve channels through the cribriform fossa or via the trigeminal nerve channels. See below rat brain diagram.[15]

[15] Danielyan, L., Beer-Hammer, S., Stolzing, A., Schäfer, R., Siegel, G., Fabian, C., ... & Novakovic, A. (2014). Intranasal delivery of bone marrow-derived mesenchymal stem cells, macrophages, and microglia to the brain in mouse models of Alzheimer's and Parkinson's disease. *Cell transplantation*,*23*(1), S123-S139.



This diagram is key for understanding how the insulin and other substances can get into the brain--in the CSF or parenchyma. One question commonly asked is, how *long* does it take for insulin or other substances to get into the brain via this intranasal delivery?

The consistent answer provided by the researchers and the studies is 10-15 minutes for the insulin or stem cells to be detected in the CSF after intranasal administration.

So, if insulin is so amazing in the brain, what do stem cells and prp do?

IN adult stem cells have been used to treat ischemic brain damage by reducing gray and white matter loss.[16] IN adult stem cells downregulate neuroinflammatory cytokines and rescue tyrosine hydroxylase (TH)-positive neurons in the substantia nigra in AD and PD patients.[17]

We do not know exactly what IN plasma does in the brain, but we have a pretty good idea. We know that there are neurosurgical researchers who have placed growth factors epidermal growth factor and fibroblast growth factors directly onto the dentate gyrus, via the ventricles, of the hippocampus after opening the skull surgically.

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[16] Van Velthoven, C. T., Kavelaars, A., van Bel, F., & Heijnen, C. J. (2010). Nasal administration of stem cells: a promising novel route to treat neonatal ischemic brain damage. *Pediatric research*, *68*, 419-422.

[17] Danielyan, L., Beer-Hammer, S., Stolzing, A., Schäfer, R., Siegel, G., Fabian, C., ... & Novakovic, A. (2014). Intranasal delivery of bone marrow-derived mesenchymal stem cells, macrophages, and microglia to the brain in mouse models of Alzheimer's and Parkinson's disease. *Cell transplantation*,*23*(1), S123-S139.

"Growth factor basic fibroblast growth factor (bFGF) or epidermal growth factor (EGF) infusion enhances injury-induced cell proliferation in the dentate gyrus (DG) and improves cognitive function in rats following fluid percussive injury."[18]

"Other studies have found that infusion of S100β or VEGF can also enhance neurogenesis in the hippocampus and improve the functional recovery of animals following TBI (Kleindienst et al., 2005; Lee and Agoston, 2010; Thau-Zuchman et al., 2010)."[19]

Neurogenesis from plasma growth factors is certainly one benefit of PRP but it also has many other benefits and possible mechanisms of action.

Autologous plasma contains growth factors and cytokines to aid the injured brain

•VEGF, EGF increases angiogenesis

•PDGF, TGF-p enhance collagen growth

•IGF-1 stimulates protein synthesis

Enhanced collagen IV in neurons of the brain has been shown to have a neuroprotective effect and reduce amyloid-beta proteins.[20]

Other studies with PRP and the brain have shown the following:

Plasma cytokines

•control inflammatory mediators cox1, cox2

•guide stem cells to areas of injury

Human plasma lysate administered to rats (via the middle cerebral artery) after ischemic stroke was shown to reduce infarct volume.[21]

The exciting, synergistic aspect of all of the plasma is the idea that PRP guides stem cells to areas of injury in the brain or elsewhere in the body. Stem cells get upregulated by certain nutritional foods, HBOT, exercise, and may also be administered. Healing the damaged, ischemic tissue of the brain involves PRP, stem cells, and HBOT in a very unique, coordinated manner. Improving uptake and usage of these factors in the brain is a key component to healing.

Protocols

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[18] Sun, D. (2014). The potential of endogenous neurogenesis for brain repair and regeneration following traumatic brain injury. *Neural regeneration research*, *9*(7), 688.

[19] Ibid.

[20] Gladstone Institutes. (2008, December 10). Collagen May Help Protect Brain Against Alzheimer's Disease. *ScienceDaily*. Retrieved March 2, 2016 from www.sciencedaily.com/releases/2008/12/081210150713.htm.

[21] Zhang, Y., Ying, G., Ren, C., Jizhang, Y., Brogan, D., Liu, Z., . . . Ji, X. (2015). Administration of human platelet-rich plasma reduces infarction volume and improves motor function in adult rats with focal ischemic stroke. *Brain Research, 1594*, 267-273.

The key protocols for using PRP and insulin are in the document entitled “Physician Instructions for 5 Day+ Treatment Program”. If possible, with time and patient permitting, Dr. Hughes is now recommending that patients get a second IN PRP/insulin/glutathione/B12 (PRP cocktail) treatment (or IN stem cell treatment) after the first treatment. Otherwise, it is advisable for moderate to severe TBI patients to get IN PRP cocktail every 2-3 weeks if completing a 40 HBOT session. If patients are local and unable to afford that consistent of PRP treatment, getting a IN PRP every 1-2 months, in combination with home HBOT, for a total of 3-4 treatments in 6 months is acceptable. For patients only present for a 3 day program, getting at least 2 HBOT dives is recommended before doing IN PRP. See “Sample Patient Protocols” for more information.

Dangers/Side Effects

Bloody noses and swallowing plasma or local anesthesia have been the biggest side-effects of IN PRP or insulin therapy. Sneezing is another danger of the treatment. If that occurs, use more If the patient swallows the PRP/insulin/nutrient cocktail, he or she may need some form of sweet substance to eat to prevent a drop in blood sugar. Otherwise, using good sterile technique will prevent infection. The key is to get the plasma into the upper third of the nose and be patient.

Nutritional Therapies and Ketogenic Diets

Overview

It is a fact that most mainstream allopathic or osteopathic physicians do not consider much beyond basic nutrition when discussing TBI patients or other patients in general. Indeed, functional medicine physicians, naturopathic physicians, nutritionists, chiropractors, acupuncturists, and lay practitioners have given more credence to the health benefits of diet and nutrition. However, for the treatment of TBI, dietary control is one of the most beneficial ways patients can impact and improve their overall health.

Application for TBI

In the clinic, IV and IN therapies allow practitioners to rapidly access the brain and body of the TBI patients. We have a few studies about the use of intranasal nutritional substances.

IN glutathione has been used to reduce oxidative stress and enhance cellular detoxification in Parkinson’s disease patients.[22] IN methylcobalamin has been shown to improve QEEG Theta activity in ADHD and autism patients.[23]

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[22] Mischley, L. K., Conley, K. E., Shankland, E. G., Kavanagh, T. J., Rosenfeld, M. E., Duda, J. E., ... & Padowski, J. M. (2016). Central nervous system uptake of intranasal glutathione in Parkinson’s disease. *npj Parkinson's Disease*, *2*, 16002.

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The Myers cocktail is the standard IV cocktail used by many functional medicine practitioners. What is so great about the Myers cocktail? The biggest factor in the use of IV nutrients is that many vitamins, minerals, and other micronutrients are cofactors for metabolic processes, which mean they protect the body from free radicals (Vitamin C), improve energy production (B-vitamins), and help eliminate waste products (glutathione). Dr. Hughes' provides these IV nutrients on a regular basis to every TBI patient as part of their treatment for TBI and overall health.

Oral nutrition is also critical for these patients, as most all modern, Western patients because most of us are deficient in primary nutrients.

Vitamin Deficiencies are prevalent in the U.S.

-97% of Americans are lacking in potassium

-70% lack vitamin D

-65% lack vitamin K

-60% lack vitamin E

-30% lack vitamin A and C

-23% lack magnesium[24]

For TBI patients, correcting vitamin deficiencies can have significant benefits. Vitamin D deficiency has been found in over 65% of TBI patients suffering from chronic fatigue.[25] B vitamin supplementation (particularly B12, folate, B6) has been found to improve memory, mood, and energy levels and has been used to prevent stroke and Alzheimer's disease.[26]

Dr. Robert Cantu, MD supports the use of optimizing energy metabolism for TBI patients in his below statement:

"The brain is in a metabolic crisis in a concussion, potassium ion from inside the cell going extracellular, calcium ions going intracellular, neurotransmitters widely released in a chaotic manner. It takes energy to pump that potassium back, put the neurotransmitters back on so the cell can function."[27]

By using nutritional substrates to the brain that correct the metabolic crisis, we can help to stabilize neurotransmitter release and repair damaged neurons. Ultimately, a TBI is a problem

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of energy metabolism. Healing from TBI requires solving that energy crisis.

See Dr. Cantu's comments on film at http://www.brainline.org/content/multimedia.php?id=9022

Oral nutrition for TBI Therapy has primarily been focused on the upregulation of stem cells and maintaining a ketogenic state for the body. Several nutrients and foods have been found to improve circulating stem cells and growth factors: blueberries, Vit D3, AFA (blue-green algae), elk antler. Patients are instructed to take these foods and supplements before and after HBOT and PRP treatment.

During IN and IV treatments, patients are given oral glycerin (2-3 tsp) mixed with MCT oil (Brain Octane 1 Tbsp) before IN or IV stem cells or plasma are introduced. Glycerin helps to make the blood-brain barrier a bit more permeable.

Patients are advised to continue on the Brain Octane (1-2 Tbsp 2x/day) and a ketogenic diet for the next 3 months. Brain Octane helps maintain high amounts of ketones in the patient's body and brain.

Ketogenic diets are a proven treatment for patients suffering from epileptic seizures. Ketogenic diets studied in brain trauma (CCI) produce corticol sparing and less apoptotic neurodegeneration and overall improvements in cognitive and motor functioning.[28]

The mechanism of how ketone bodies work to help TBI patients is diagramed below. It is theorized that ketones work because they increase the available calming neurotransmitter GABA, thereby reducing neuronal hyperpolarization and the excitatory neurotransmitter glutamate. With less glutamate, there is less oxidative stress and improved neuroprotection.

In simple terms, a brain with more protection from the rapid oxidative stress from an increased need to heal metabolically makes ketones the ideal fuel for an injured brain. More GABA production means a calmer brain with slower more healing brainwaves available to restore the brain to its balance.

[28] Stafstrom, C. E., & Rho, J. M. (2012). The Ketogenic Diet as a Treatment Paradigm for Diverse Neurological Disorders. *Frontiers in Pharmacology*, *3*, 59. http://doi.org/10.3389/fphar.2012.00059.

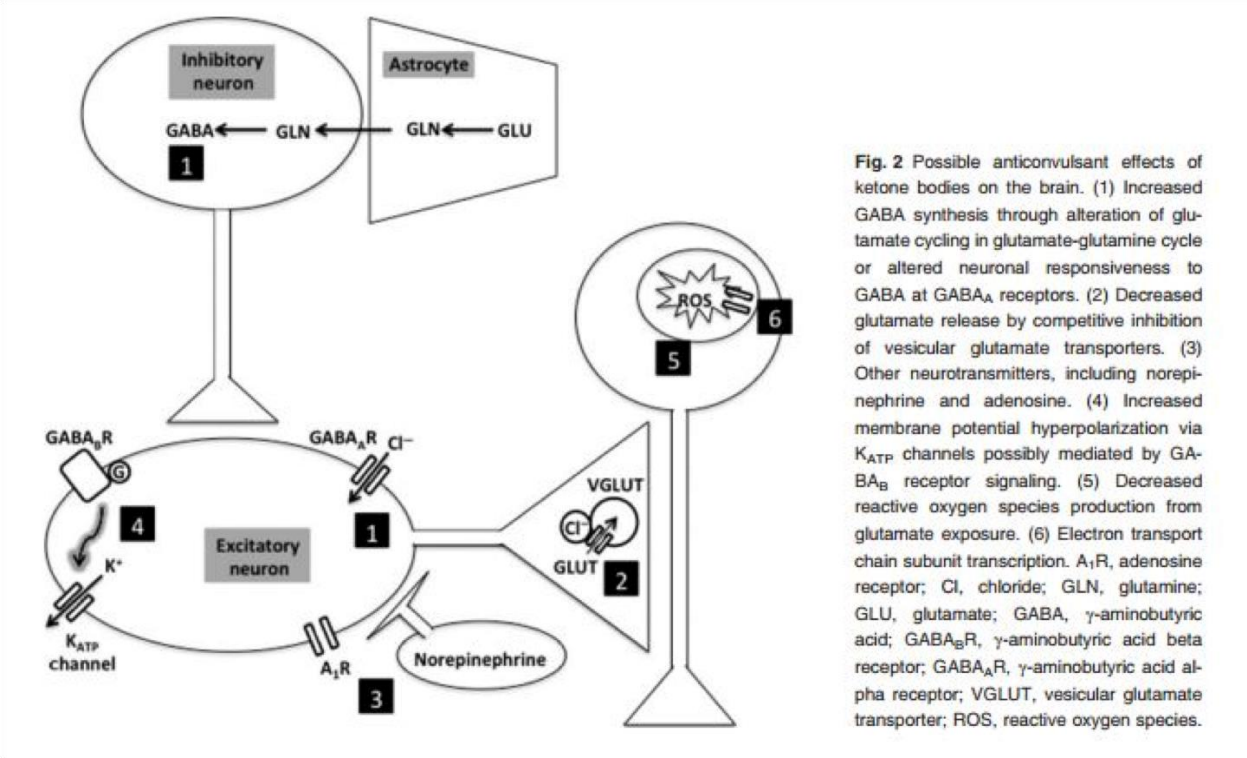

Fig. 2 Possible anticonvulsant effects of ketone bodies on the brain. (1) Increased GABA synthesis through alteration of glutamate cycling in glutamate-glutamine cycle or altered neuronal responsiveness to GABA at $GABA_A$ receptors. (2) Decreased glutamate release by competitive inhibition of vesicular glutamate transporters. (3) Other neurotransmitters, including norepinephrine and adenosine. (4) Increased membrane potential hyperpolarization via K_{ATP} channels possibly mediated by $GABA_B$ receptor signaling. (5) Decreased reactive oxygen species production from glutamate exposure. (6) Electron transport chain subunit transcription. A_1R, adenosine receptor; Cl, chloride; GLN, glutamine; GLU, glutamate; GABA, γ-aminobutyric acid; $GABA_BR$, γ-aminobutyric acid beta receptor; $GABA_AR$, γ-aminobutyric acid alpha receptor; VGLUT, vesicular glutamate transporter; ROS, reactive oxygen species.

McNally, M. A., & Hartman, A. L. (2012). Ketone bodies in epilepsy. *Journal of neurochemistry*, *121*(1), 28-35.

Dangers and Side Effects

Several patients report some detox symptoms from getting IV nutrition so be aware and go slower with IVs if you suspect these types of patients. Other patients may need more nutrition include supplements to aid with heavy metal detoxification, hormone balancing, etc. TBI Therapy takes a very focused approach to its protocols with the forethought that many patients may need more than just the specific nutrients or drugs discussed.

MCT oils can be derived using hexane so be aware of which brands you may select for your patients. We have found Brain Octane to be pure from this toxic processing. Of note, Brain Octane is more than just coconut oil...it is 16x more concentrated in ketones. Because of that fact, it may upset some patients stomachs so Dr. Hughes recommends taking with some food.

See the "Ketogenic Diet" (By Dr. Scott Sherr) addendum for more information. Also see http://tbitherapy.com/tbi-protocol-references/ for more research on ketogenic diets and brain injury.

Adjunctive Therapies

There are many other therapies that are utilized or recommended by TBI Therapy for certain patients including Brainwave training with binaural rhythms, EEG Biofeedback, Neurofeedback, TMS, LLLT (low level laser therapy), the PoNS treatment, acupuncture, massage, float tank, ozone sauna therapy, yoga, meditation, but we have not included these in our basic training protocol. Other practitioners may feel it is vital to include these in the protocol but be advised that TBI patients can get easily overwhelmed with too many items to do over a given period of time. Patients who have more time or less severe of injuries can add some more modalities to their overall protocol. Feel free to contact Dr. Hughes for any questions you may have about these incorporating these adjunctive therapies into your patient's regimen.