Autonomic signaling in chronic cerebrospinal venous insufficiency:

A perivascular approach for vasodilation of the internal jugular vein

INTRODUCTION

Multiple sclerosis (MS) is a disease characterized by demyelination of axons and chronic inflammation in the cerebral and spinal cord. Patients are affected at any age and are mainly female. MS has several forms, though most patients have the relapsing and remitting mode of the disease. Currently, ***no findings or speculation has been made about the etiology of the relapsing and remitting mode of MS.*** In the early phase, MS is often associated with autonomous dysregulation, such as thermoregulatory imbalances (i.e., hot and cold sensations, chills, diaphoresis), bizarre dreams, tachycardia, fatigue, and migraine headaches. In its progressive form, MS may present with dysesthesia of the upper and then lower extremities, starting on the left side of the body and progressing in some cases to loss of gait. Eventually, gross architectural damage occurs with regionalized and profound results. Imaging studies show exacerbation of white matter lesions during the flare ups and in the relapse phase **(1).** Diagnostic MRI studies of the brain show hyper-intense white matter in axials T1 and T2**.** Other autoimmune diseases with inflammatory causes also have been identified proceeding brain pathologic symptoms. In most of those cases, MRI shows disseminated lesions in white and gray matter **(2).**

Several cells in the brain play a major role in inflammatory and immune response processes. Microglia function as macrophage cells in the brain. They regulate CNS innate immunity and initiate appropriate responses, such as inflammation. In the brain, this inflammatory response is called neuro-inflammation, and it is a fundamental response generated to protect the CNS; however, uncontrolled or prolonged neuro-inflammation is potentially harmful and can result in cellular damage and cell death. Cell death and the products of damaged neurons and neuroglia in the brain may initiate an autoimmune reaction to protect the rest of the brain.

Literature from the International Society for Neurovascular Disease, results from the liberation procedure and from other laboratory research, as well as our curiosity, encouraged us to study MS and chronic cerebrospinal venous insufficiency (CCSVI).

Current broad-spectrum studies by Paolo Zamboni of the International Society for Neurovascular Disease pioneered recently identified stenosis of the internal jugular vein and blockage of the venous outflow as potential concomitant pathologies, if not the single cause, of MS. The liberation procedure provided significant relief of MS symptoms **(1)** compared to traditional treatment with immunotherapy such as intravenous immunoglobulin, corticosteroids, cyclophosphamide, and rituximab. We have been encouraged by enthusiastic patients and advocates to propagate the liberation procedure. However, the therapeutic implications of negative results with immediate relapse, as reported in internet media, have led to switching the approach toward an extra-luminal path of venous dynamics.

*subependymal veins connect the lateral venous group (in blue) and exit the cranium through the condyloid vein**(*)**

OBJECTIVES

- To measure the efficacy and safety of administering dexamethasone, lidocaine, and thiamine by using an extra-luminal, perivascular approach in the internal jugular vein (IJV) bilaterally in patients diagnosed with chronic cerebrospinal venous insufficiency (CCSVI);
- To assess the treatment impact on patients' blood flow and veno dilation of the IJV, as measured by cognitition status, speech pattern , mobility, and daily living activity; and
- To evaluate the accessibility of IJV by perivascular and cervical paths.

METHOD

Venous drainage from the brain occurs through the pair of internal jugular veins and the basilar vein. Sudden, phasic stenosis of the main blood outflow may hinder appropriate and physiologic blood drainage from the brain. This stenosis causes retrograde flow of venous blood into the brain's vessels, which decreases oxygen levels in the brain and exposes neurons to continuous low (70%–75%) oxygenation levels and toxic metabolites. Stagnation of veins at the capillary level may cause extravasation of metabolites and iron molecules from apoptosis of erythrocytes in the perivascular space. Diminished oxygen delivery to the brain results in cerebral ischemia that is not compatible with healthy brain function. Thus, our concept included the following:

- Review anatomy and morphology of cerebral-cervical venous integrity;
- Based on our hypothesis of autonomic nerve involvement in the vein behavior;
- Increase the number of ultrasonographic Doppler studies to four in subsequent weeks;
- Predict an extra-intimal, perivascular approach to internal jugular vein treatment; and

- Use a treatment formula containing dexamethasone, lidocaine, and thiamine, based on our past trigeminal neuralgia and migraine treatment experience.

Study Period

The index date for the study period is defined as the day that the first patient was diagnosed by reviewing the medical records for non-MS and MS patients in our clinical setting. All patients but one had already exhausted immunotherapy and the liberation procedure in California, and all experienced exacerbation of MS symptoms between June 1, 2007 and September 2013. Study follow-ups occurred at 1 week, 4 weeks, 26 weeks, and 52 weeks.

June 1, 2013 December 30, 2014

Study Sample and Criteria

- Patients were selected randomly by approaching our clinic and by referral from patient advocates. All sought treatment for acute exacerbation or status quo of MS symptoms;
- All patients had profound diagnosis and imaging studies of MS by neurologists;
- All patients and caregivers were informed about the treatment approach, the medication, and the speculative nature of the research;
- Patients received four subsequent Doppler studies of the IJV at our clinic to verify the level of IJV stenosis and the presence or absence of blood flow (% of speed) and to rule out other causes of IJV vasoconstrive disease in the presence of similar neurologic symptoms;
- All patients, spouses, and caregivers were able to verbalize and sign the protocol consent and present at the time of procedure;
- All patients agreed to participate in follow-up visits and communication for a minimum of 12 months, and all agreed to the use of their data for scientific use;
- The study had no medical comorbidity discrimination.

Exclusion Criteria

- Other neurological cerebral inflammatory disease, such as encephalitis, or other known autoimmune diseases
- History of myocardial infarct, known cardiac ischemia, stroke, TIA, or seizure activity
- Hypersensitivity or allergy to any components of the implemented formula
- Under age (no children were included)

Outcome and Statistical Results

- Between June 2013 and December 2014, four patients qualified for the treatment. Two patients had undergone a liberation procedure, two patients were wheelchair-bound, one patient was misdiagnosed with Alzheimer's dementia at an early age, and one patient was never diagnosed with MS but met similar neurological and imaging criteria. All patients had MRI evidence of MS lesions and magnetic resonance venography evidence of IJV stenosis. One also showed questionable thrombosis of the left sigmoid vein of the cerebral vein.
- Three patients received treatments at 4, 8, and 12 weeks. One received treatments at 4 and 8 weeks only.
- Two patients used wheelchairs for musculoskeletal stiffness, such as frozen shoulder, pelvic-hip girdle insufficiency, and muscle weakness. They were provided with

hydrotherapy, physical therapy, and speech therapy after treatment.

- One patient interrupted physical therapy and follow-ups because of a lack of social support. A Doppler study was performed prior to and 30 minutes after procedure. Vitals were checked every 10 minutes. Continuous EKG monitoring, IV access (NS), and pulse oximetry were provided. One gram of ceftriaxone (IV push or IM) was administered one hour prior to the procedure.
- The procedure was performed in a sterile, surgical fashion.

CASE REPORT AND RESULTS

Patient # 1

This patient was a 55-year-old male. We suspected the presence of CCSVI and misdiagnosis of Alzheimer's dementia in October 2011, because the patient had experienced fluctuating, crawling neurological and cognitive symptoms since 2005. PET and MRI of the brain in 2011 and 2012 originally revealed decreased glucose metabolism in the temporoparietal and frontal regions and the posterior cingulate gyrus. Intensive neurological examination did not reveal the expected biomarker for Levi bodies or amyloids. Following liberation venoplasty on November 02, 2011, in California, the patient's cognitive capacity tremendously improved and his speech improved. Within three months, however, he reverted to the previous level. Extensive, weekly Doppler studies revealed re-stenosis of the IJV to the same level as prior to venoplasty. Numerical values were almost the same as they were before treatment. Cognition, speech, urinary and fecal incontinence, and gait returned to the same levels.

From 2012 to February 2013, the patient was referred to major university centers in California, where he received stem cell therapy, nutritional advice, and Cannabis inhalation therapy. In 2013, encouraged by studies at the International Society for Neurovascular Disease and by results from the liberation procedure, we discussed a perivascular approach with the patient and his family, who agreed to the minimally invasive trial. We used the same material, based on our successful results for migraine treatment. On March 2, 2013, our team completed the first empiric approach. We witnessed IVJ dilation of 50–60% and improved venous flow within a week after treatment. Positive behavior and cognitive changes were observed. Six months later, on September 9, 2013, we repeated the re-stenosis treatment. We verified IVJ blood flow patency and caliber dilation by Doppler ultrasound at 1, 3, and 6 months. Prior to treatment, we obtained magnetic resonance venography with contrast at the same imaging center, and it demonstrated improved caliber of the lt. jugular vein, compared to the July 7, 2012, studies. However, it also showed persistent focal narrowing and short segment occlusion at the C1 and C2 levels bilaterally. MRI of the brain showed no significant interval changes. From September 2, 2013, to August 26, 2015, the IJV caliber remained mostly open. Blood flow stayed between 60–70% while supine and 80–90% while upright bilaterally in all Doppler follow-up examinations. The patient's loss of speech (80–90%), cognitive deterioration, and daily life incapacitation unfortunately remained the same.

Patient # 2

The patient was a 57-year-old, white female with symptomatic transverse myelitis diagnosed in 1989 and secondary progressive multiple sclerosis diagnosed in 1992. She was not responsive to conventional treatments, and neurologic symptoms had confined her to bed. On February 4, 2010, she received venography and balloon dilation for CCSVI at the University of California, Davis. She visited our clinic for migraine treatment in June 2013. She and her spouse were introduced to perivascular signal modification in INJ. By February 9, 2014, she had received three serial treatments and showed substantial improvement in mobility, including use of her upper extremities and use of a walker. Progress continued until April 2016. Venous blood flow maintained between 80–90% bilaterally, and vasospasticity improved 70–80% by periodic control of ultrasound Doppler imaging.

Patient # 3

This patient was a 39-year-old African (native) female who was diagnosed with MS and exhibited severe neurological symptoms for 11 years. A serial MRI of her brain on May 17, 2011, revealed progressive extensive hyperintense signals throughout the visible spinal cord, indicating active demyelination. She did not respond to conventional treatments, and neurological symptoms confined her to bed. The patient was referred to our trial by a CCSVI patient advocate. Treatment started on June 11, 2014, and she received two treatments within 6 months. Periodic Doppler ultrasound imaging revealed improvement in vasodilation of 50–70%, and venous blood flows of 100% in the supine and 90% in the upright positions. After the second treatment, she could move her upper and lower extremities during hydrotherapy; however, severe frozen pelvic and shoulder girdle compromised mobilization. Family and social support issues interrupted the continuation of her treatment.

Patient # 4

The patient was a 52-year-old white female with early neurologic symptoms of MS diagnosed at our clinic. An MRI of her brain was conducted by her neurologist on January 29, 2014, and showed periventricular and subcortical white matter foci consistent with chronic micro-angiopathic disease. Magnetic resonance venography of her brain and extracranial veins on April, 17, 2014, revealed near complete loss of flow in the left transverse sinus, caused by suspected hypoplasia of the left jugular bulb and IJV. Additionally, the left IJV was not visualized because of suspected congenital hypoplasia or chronic thrombosis.

She and her spouse were introduced to perivascular signal modification of the IJV. She received serial Doppler studies, and anatomical stenosis and venous blood flow were measured. On May, 24, 2014, and December 13, 2014, she received treatments per our trial protocol. The last post-treatment Doppler ultrasound was performed on February, 18, 2015, and showed between 30–40% dilation, visibility of the left IJV, and measureable venous flow of 80–90% in the supine and 40–50% in the upright positions.

Vasodilation of approximately 30% in the left IJV was achieved. The right IJV demonstrated satisfactory results. The patient was then lost because of non-adherence.

DISCUSSION

The tunica adventitia comprises the outer layer of most blood vessel walls and has histologically been regarded as a loosely organized collection of fibroblasts, perivascular autonomic nerves, and micro-vessels embedded in a collagen-rich extracellular matrix. The tunica adventitia is the target organ of the sympathetic and parasympathetic nervous system when responding to physical and biological stressors. **The autonomic nervous system may trigger signal modification in the adventitia "from the outside in" during vascular injury and consequent neurological disaster.** Physiologic studies show that autonomic nerve fibers penetrate the adventitia and proliferate into the contractile, smooth tunica muscularis layer, but not into the intima, which does not demonstrate direct nerve supply per se.

Recent studies suggest a more complex and dynamic picture of the adventitia that emphasizes critical roles played by interacting adventitial cell types in growth, inflammation, and repair of diseased vascular walls. The normal adventitia contains resident macrophages, mast cells, T cells, B cells, and dendritic cells, and it is a major site for immune surveillance and innate immune responses **(4)**. The biologic processes of inflammatory reaction and induction of genetic coding appear to take place at the local level, rather than systemically. The major effect of binding to DNA is the suppression of transcription by opposing the activation of the transcription factors AP-1 and NF-κB, which induce gene expression encoding in nearly all pro-inflammatory cytokines **(5)**. Glucocorticoids also suppress expression of inflammatory genes that encode T cell growth factors, such as IL-2, IL-4, IL-15, and IL-17, as well as interferon-γ **(6)**. Additionally, glucocorticoids reduce expression of genes encoding COX-2, inducible nitric oxide synthase, and intracellular adhesion molecule-1, which are normally induced by cytokines IL-1 and TNF-α. Glucocorticoids increase expression of genes encoding anti-inflammatory molecules, such as the cytokine IL-10 and the IL-1 type 2-decoy receptor **(7)**.

Physiologically, adventitia may play a more important role than the endothelium in the venous system. The tonic vasoconstrictive-vasodilatory behavior of human veins during activity is mostly represented in cardiac rhythm. However, it misses the permanent, rhythmic, and diastolic blood pressure of arteries and the respective, multipotent, arterial, and intima physiology. Like most tissues, blood vessels have intrinsic mechanisms for repairing injured or diseased tissues. This capacity for repair of the artery and vein walls allows continuous function **(3)**. The adventitia of large and medium arteries is physiologically undermined by the stronger muscularis media, which absorb ventricular pulse pressure and dampen the propagation of the pulse pressure gradient **(8)**. This is accomplished by expanding the elastic fiber-containing artery wall and relaxing with each heartbeat. The largest changes in wall diameter occur in the outer layers (e.g., the adventitia). These mechanisms are regulated directly by sympathetic and parasympathetic impulses, which maintain vessel integrity and internal equilibrium in mammals.

Schematic of the adventitial influence of vascular function. A: Adventitial fibroblasts (shaded oval cells) may be transfected via adenoviral vectors to produce nitric oxide (NO) upon receptor or non-receptor activation. Superoxide anion ( ), produced by NADPH oxidase in the adventitia (Ad), limits the magnitude of NO-mediated relaxation. Norepinephrine (NE); endothelial NO synthase (eNOS). B: Sympathetic and vagal efferent nerve terminals are located in adventitia. Released neurotransmitters may act on vascular smooth muscle directly or by releasing endothelium-derived NO. Acetylcholine (ACh). C: Adventitial fibroblasts migrate to the endothelial cell (EC) and smooth muscle (VSM) layers to participate in proliferative processes leading to intimal thickening and atherosclerosis **(9)**.

In summary, our approach to stenotic diseased IVJ in CCSVI included minimally invasive chemical stimulation of the tunica adventitia. Our results show that IJV with stenotic disease may produce genetic modification of progenitor or other cells of tunica adventitia cells in CCSVI, thus revitalizing the adventitia integrity to a functional level. The combination of dexamethasone, lidocaine, and thiamine in this procedure as genetic modifier is safe and efficacious, procedure path is less aggressive compared to venoplasty and placement of self-retracted stents. This approach may offer more promising results if combined with guided imaging support. This algorithm produced clear vasodilatation and venous flow when it reached the perivascular environment appropriately. This approach also may facilitate a new hypothetical approach to CCSVI treatment involving genetic modification of impaired signals and differentiation of myofibroblasts at the level of tunica adventitia, and consequently, of the tunica muscularis media **(3)**.

CONCLUSION

It is well demonstrated that the brain tissue is 100% oxygen- and glucose-dependent. Any reduction in the oxygen supply of the brain tissue either induced by acute ischemic reperfusion or by a chronic process, is a major contributing factor to tissue damage. Neuro-inflammation, as with all inflammation, is a fundamental response that is genetically programmed to protect organs from endogenous or exogenous harmful factors. In the brain conglomerate, "many scavenger receptors (10,11), microglia (as well as CNS cells, such as astrocytes) are able to recognize harmful stimuli and respond by producing inflammatory cytokines such as TNF-α, IL-6, IL-1β, interferon-γ, and several chemokines (9,12). "**(7).**

The response of the autonomic nervous system to internal and external stimuli is an independent process. It expresses its action by genetically modifying biologic signals over the adventitia complex of widely distributed blood and lymphatic vessels. Its malfunction causes many disorders in vertebrates, including CCSVI. CCSVI in MS patients may be activated by transmitted signals from autonomic ganglia and cerebral nuclei to tunica adventitia directly by induction of hypoxia. The neuro-inflammatory mechanism in response to autonomic volatile stimuli may result in periodic dilation and constrictive behavior of the medium and large veins, thus empowering the volume pressure ingredient**(9).** Because MS features a broad spectrum of clinical and histological manifestations, the cause is not consolidated yet as a disseminated systemic. We speculate that relapse and remission in MS may correspond to the tonic vasospasm

of the IJV, the vertebral vein, and the azygos vein in CCSVI. However, further investigation should assess correlation with the autonomic ganglia and other possible factors in CCSVI –MS complex. Further, early recurrence of vasospasm after the liberation procedure in CCSVI patients requires critical multidisciplinary interaction and implementation of new perspectives to promote the discovery of a cure for this devastating disease.

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