POTENTIAL AMELIORATION OF GLYMPHATIC FUNCTION IN PROGRESSIVE SUPRA NUCLEAR PALSY

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ABSTRACT

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Neurodegenerative conditions like Progressive Supra Nuclear Palsy can be one of the most challenging conditions for patients and their families. Early education regarding why this condition develops and how it progresses may be the key to helping delay or even stop this Progressive Neurodegeneration. With current knowledge regarding the potential for successive trauma to permanently damage the glymphatic system we can better prepare for the resulting manifestation of chronic traumatic encephalopathy. With more understanding of how the accumulation of tau proteins is linked to neurodegenerative conditions such as Supra Nuclear Progressive Palsy, there are more possibilities to treatment plans using Osteopathic Manipulative Techniques. With OMT techniques, direct meningeal treatment to allow for correction and potential rehabilitation of this glymphatic system could reduce the amount of unnecessary development of these cases. Although there is no evidence to support that Progressive Supra Nuclear Palsy can be reversed. There is enough data now to consider modalities that help in the lymphatic drainage as a means of helping slow the progression of what is only a terribly debilitating condition.

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INTRODUCTION

As neurodegenerative diseases continue to remain prevalent among our aging communities, the scientific communities have yet to establish exact causes for these debilitating conditions. As certain conditions are more studied than others, there is significant data suggesting that there may be a lymphatic dysfunction at the root of some of these conditions. At least in conditions such as Alzheimers and Progressive Supra Nuclear Palsy, there is evidence that supports that these conditions may actually develop as a result of tau protein accumulation giving them the categorization as tauopathies. This accumulation of tau proteins in the brain has been suggested to be a major contributing factor in the development and progression of neurological brain degenerative conditions we are faced with today (Iliff et al, 2012). If this is in fact the case, then there may be potential to hinder the progression of neurological decline by deterring the build-up of these proteins to begin with.

In this paper, we shall examine the current processes by which neurological conditions such as Progressive Supra Nuclear Palsy develops, present current literature surrounding brain lymphatic function, explore current treatment protocols, we will then provide our own personal case study and finally suggest the benefits of osteopathy as a potential treatment method for improving glymphatic function in both healthy and non healthy individuals.

PROGRESSIVE SUPRA NUCLEAR PALSY

Progressive supranuclear palsy (PSP) is an uncommon degenerative neurological disorder that causes progressive impairment of balance and walking; impaired eye movement, abnormal muscle tone (rigidity); speech difficulties (dysarthria); and problems related to swallowing and eating (dysphagia). Affected individuals frequently experience personality changes and cognitive impairment. Symptoms typically begin after age 60 but can begin earlier.

Although experts basically understand how Progressive Supra Nuclear Palsy happens, they don't understand why it happens. PSP occurs when brain cells in an area of the brain stem become

damaged, but how and why these cells are damaged isn't clear. The exact cause of PSP is unknown, but research suggests that it involves a gradual deterioration of brain cells in a few specific areas in the brain, mainly in the brain stem.

Currently, there are no tests or brain imaging techniques to definitively diagnose PSP. An initial diagnosis is based on the person's medical history and a physical and neurological exam. Identifying early gait problems, problems moving the eyes, speech and swallowing abnormalities, as well as ruling out other similar disorders is important. Diagnostic imaging may show shrinkage at the top of the brain stem and look at brain activity in known areas of degeneration.

The hallmark of PSP is the accumulation of abnormal deposits of the protein tau in nerve cells in the brain. These deposits cause the cells to malfunction and die, which stops the flow of information to other nerve cells. The accumulation of tau puts PSP in the group of disorders called *tauopathies,* which includes Alzheimer's disease, corticobasal degeneration, and some forms of frontotemporal degeneration.

The PSP Association based in UK has outlined four stages as can be found online via the brain support network.

Early stage:

May present via the fracture clinic, falls services, eye specialist or speech and language therapist. The early stage typically spans years 0-1.

- Ambulant.
- Occasional falls.
- Unsteadiness and poor balance.
- Possible visual problems affecting ability to read.
- Voice changes, for example reduced volume.
- Mood changes.
- Reduced socialising.

- Changes in mood and behaviour, including apathy and anxiety.

Mid stage:

Many people reach this stage before diagnosis. Consider discussing advance care planning and advance decisions to refuse treatment. Consider referral to palliative care services. The mid stage typically spans years 2-3.

- Ambulant with aids.
- High risk of falls and injury.
- Visual problems affecting self-care abilities, for example eating and walking as unable to move eyes to see.
- Speech increasingly unintelligible.
- Inability to initiate conversation.
- Impulsivity (risky or impulsive behaviour).
- Apathy.
- Dysphagia.
- High level of supervision required.
- Increasingly socially withdrawn.

Advanced stage:

Patients should be on GP palliative care register and have access to specialist palliative care.

The advanced stage typically spans years 3-6.

- Mobility significantly compromised, probably chair bound requiring a wheelchair for mobility.
- Significant visual problems.
- Significant muscle stiffness.
- Significant communication problems, but probably still able to understand.
- High risk of aspiration and pneumonia as a result of dysphagia.

- Pain.
- Increasing periods of sleepiness.
- Incontinence.
- Severely withdrawn socially.
- Dependent for most or all aspects of care.

End of life stage:

This stage is difficult to detect, but may be indicated by reduced levels of consciousness, inability to eat or drink, acute infection, a fall or major fracture, and rapid and significant weight loss. The end of life stage typically spans 6-8 weeks.

- Severe impairments and disabilities.
- Rapid and marked deterioration in condition.
- Decisions with regard to treatment interventions may be required, considering an individual's previously expressed wishes (advance decisions to refuse treatment).

GLYMPHATIC SYSTEM

For years, there has been a belief among scientific communities that there is no lymphatic function of the brain but as of 2012, this belief has been proven incorrect. Researchers found lymphatic vessels in the brain independently of each at both the University of Virginia in Charleston and the University of Helsinki in Finland.

Previously, it was believed by most that the CNS was devoid of a lymphatic system however now there is direct evidence of intraparenchymal waste products in the CSF being cleared through fluid channels in the meninges. Until the last 8 or so years, the brain glial lymphatic system was suspected to account for a minor portion of this CSF drainage. This system has been since called the glymphatic system.

Here define the glymphatic system as a brain-wide network of paravascular channels, along which CSF moves into and through the brain parenchyma, facilitating the clearance of interstitial solutes, including amyloid-β, from the brain.

This newly discovered glymphatic system of the CNS demonstrates that astrocytes facilitate the clearance of cerebral parenchymal waste and resultant interstitial brain edema through the pulsations of CSF along perivascular spaces between deep penetrating cerebral blood vessels, leptomeningeal sheaths, and aquaporin-4 (AQP4) water channels that drain into the cervical lymphatics (Illif et al 2012).

The connection between the central glial lymphatic system and the peripheral lymphatic system is found within the meninges where CSF is absorbed. Here, the waste products of the brain parenchyma and CSF move into the fluid channels of the meninges and into the peripheral lymphatic system (Louveau et al, 2017)

Specifically in a study by Iliff et al (2012) Researchers demonstrate that a substantial portion of subarachnoid Cerebrospinal fluid cycles through the brain interstitial space. These researchers used vivo two-photon imaging of small fluorescent tracers to show that CSF enters the parenchyma along paravascular spaces that surround penetrating arteries and that brain interstitial fluid is cleared along paravenous drainage pathways.

Before these studies, it was unclear how extracellular proteins were cleared by the brain. What was made clear was that cerebrospinal fluid functions as a drain for brain extracellular solutes, but it is not yet clear how solutes from the brain interstitium move from the parenchyma to the CSF.

In two of these studies (Kashyap et al, Iliff et al) suggestions were made that the dural lymphatic network may be the mechanism for the clearance of larger molecules such a tau proteins, which have been associated with Alzheimer's disease and progressive supra nuclear palsy.

Considering what we now know about the regulation of extracellular levels of proteins and their involvement in neurodegenerative conditionsts we feel we can suggest that the impairment of this process could very well be linked with the condition itself.
This theory regarding the relationship between the two systems and that their malfunction may underlie some neurological diseases has also been speculated by Louveau et al (2017) in their article.

Illiff et al (2014) went on to prove this very theory in their comprehensive work on field mice. Their findings suggest that chronic impairment of glymphatic pathway function after traumatic brain injury may be a key factor that renders the post-traumatic brain vulnerable to tau aggregation and the onset of neurodegeneration.

In their study, they demonstrated that in mice, extracellular tau is cleared from the brain along these paravascular pathways that make up the glymphatic system. Interestingly enough they found after a traumatic brain injury, glymphatic pathway function was reduced by 60%, with this impairment persisting for 1 month.
This involved but was not limited to slowing the clearance of interstitial solutes from the brain parenchyma in this period. Any inhibition of this system after 1 month, needs still to be investigated.

CURRENT TREATMENT PROTOCOLS

When looking for current treatment protocols around PSP, we turn to both journal literature and to websites available to current PSP patients and their families.
Current Treatment Protocols in Canada involve predominantly allopathic means with alternative medicines such as Osteopathy absent from any recommended treatment protocols.
In Canada, the primary route for PSP patients is a prescription of levodopa for PSP sub-types that exhibit Bradykinesia, rigidity, and tremors. Even though these existing treatments of PSP have minimal to no lasting effects with the only effective agent being levodopa with a modest improvement in only 20% of the treated individuals (Kompoloti et al, 1998).

Studies of dopaminergic agents aside from levodopa have shown minimal to no benefit in PSP. Botulinum toxin, is sometimes injected into muscles around the eyes, to treat excessive eye closing.

There was one promising study that involved three cases of PSP receiving brain stimulation. The study used low-frequency stimulation to high-frequency stimulation in a surgical operation. Results showed the most promise of improvement in all three cases. There was a reduction of falls and an amelioration of postural balance. The patients required less assistance for daily living activities and reported an improvement of 20-36% even up to 12 months after the operation (Servello et al, 2014).

All support for patients of PSP were around a confirmed diagnosis. There was no information found regarding the prevention of PSP.

OSTEOPATHY TREATMENT

Osteopathic practitioners who use cranial osteopathic manipulative treatment have long found that using manually guided techniques can aid in the correction of movement and subsequent flow of cerebral spinal fluid.

Cranial OMT is a complementary treatment for a variety of neurological disorders but is most often used for traumatic brain injury. Expanding upon earlier scientific research on the rhythmic movement of spinal fluid during operations of the spine, osteopathic physicians theorized that by applying gentle pressure to cranial sutures, the protective layers which control spinal fluid movement could be relaxed. Dr. Upledger, an osteopathic physician, further developed and expanded this treatment into modern Craniosacral therapy. For the past 30 years, craniosacral therapy has been widely available throughout Canada and internationally.

Through Cranial Therapy, osteopathic practitioners seek to restore the “normal flow” of cerebrospinal fluid throughout the central nervous system - from the brain to the end of the spinal cord. The treatment consists of manipulation of the skull bones and articulations of the spinal column. The gentle movement of these bones is said to improve the flow of cerebrospinal fluid by manipulating the meninges which protect the brain and spinal tissue and remove any blockages and restrictions. It is thought that this movement provides restoration of the natural movements of cerebrospinal fluid (CSF) “flow”. The return to natural CSF flow is believed to restore balance to the central nervous system and put the body in a parasympathetic state.

While the exact mechanism of craniosacral therapy is not very well published, it can potentially be related to the workings of the newly discovered glymphatic system. The glymphatic system as we have discussed earlier is the lymphatic system of the brain which clears out cellular waste and other materials from the cerebrospinal fluid. The improper functioning of the glymphatic system may lead to inflammation. Traumatic brain injury (TBI), by definition, involves the neuroinflammatory response to injury. Although the mechanism is unknown, craniosacral therapy is believed to help relieve this inflammation by draining inflammatory cytokines.

Among other OMT Techniques is a list of ten techniques compiled by Hitscherich et al(2016). The OMT techniques emphasized by this group aim to alter brain arousal, augment drainage by means of body posture, and improve respiratory patterns. With a more global approach, these considerations address restrictions throughout the body, improving posture and respiration and enhancing lymphatic drainage.

Table.

Osteopathic Manipulative Treatment Techniques to Promote Lymphatic Drainage

Technique	Tissue Targeted
Thoracic outlet release	Cervical thoracic diaphragm
V-spread	Occipitomastoid suture and jugular foramen
Jugulodigastric release	Cervical lymph nodes
Clavicle muscle energy	Cervical lymph nodes
Parietal lift	Parietal bone and tentorium cerebelli
Venous sinus drainage	Occipital transverse, straight, superior sagittal, saggital (metopic suture) sinuses
CV-4	Floor of the fourth ventricle
Doming of the diaphragm	Thoracic diaphragm
Drainage along the SCM	Cervical lymph nodes
Thoracic pump	Rib cage, thoracic duct, and right lymphatic duct

Abbreviations: CV-4, compression of the fourth ventricle; SCM, sternocleidomastoid muscle.

RESEARCH OF OMT ON GLYMPHATIC FUNCTION

With more and more research emerging regarding the possibilities of Osteopathic Manipulative Treatment (OMT) on glymphatic function, there lies a potential future for non invasive, non pharmacological management of neurological disorders. However this research pile is still small, and more initiatives need to take place in order to reveal just how exactly OMT can influence glymphatic function.

There are several studies agree that any OMT treatment to the glymphatic system should have four goals. The first being to open myofascial transition areas, the second to maximize diaphragmatic movement, the third to augment lymphatic flow and fourthly to mobilize fluid in the lymphaticovenous system (Hitscherich et al, 2016).

With the correctly applied OMT techniques, there is a potential for trained Osteopathic therapists to provide non-pharmacological treatments for patients with neurological disorders.

Many suggest the possible application of osteopathic cranial manipulative medicine procedures as possibly having effects on CSF functions of waste removal. In order to be effective approaches the need to prevent the deposition of aggregation-prone proteins and/or coincidently accelerating the clearance of amyloid- B and tau from the brain (Illif et al, 2012) .

The goal of a 2021 study by Kashyap et al, was to assess the effect of osteopathic manipulative Treatment on peripheral and central glial lymphatics in patients with severe traumatic brain injury. The study assessed cerebral spinal fluid drainage and optic nerve sheath diameter which were measured by ultrasonography and a pupilometer before during and after treatment.

From a total of 11 patients, the study's findings demonstrate that OMT may help enhance glial lymphatic filtration of the cerebral spinal fluid, improve interstitial waste removal and reduce brain edema. As traumatic brain injury is a disease in which the clearance of cerebral spinal fluid and the proper functioning of the brain's glympathic system is crucial, using similar techniques should be considered in other brain-specific diseases. The results of this study should encourage the exploration of the effectiveness of OMT in diseases such as Alzheimer's and PSP.

Of particular note in this study was that with successive trauma, particularly during the acute and subacute phase, prolonged recovery can cause permanent damage to the glymphatics, which may manifest later in life through the development of chronic traumatic encephalopathy (CTE), as well as increased Tau proteins and beta-amyloid plaques, as seen in tauopathies.

ANECDOTAL CASE STUDY

It is in my experience, that in the few PSP cases I have encountered, a common element in the patient's history was a traumatic event that occurred directly to the cervical spine/and or brain. One of these patients, had their close relatives report that ever since the incident, which involved a motor vehicle collision she started to lose her balance, eye motor control, and ability to hold herself upright. By the time this patient got to my practice, she was already in the advanced stage of the illness. At this point, there was little I could do but offer a little bit of relief to the subsequent intracranial tensions.

Another patient of mine was involved in a serious motor vehicle collision as a teenager and then another traumatic spinal injury later on in life that cascaded the progression of her condition. She was diagnosed with Progressive Supra Nuclear Palsy, stage three.

In both patients, significant deterioration of tissue was felt around the brain stem.

In the second patient, it was as if the tissue of the cerebellum was hollowed out and the subsequent inferior pull of the dura created a constriction around the brain stem. Of note was that in this patient, there were dural restrictions in the cervical spine that created the sensation of anchor points which restricted the mobility of the dura as it proceeded cephalad toward the brain stem.

Although I first met this patient well into the mid-stage of the illness, there was quite a bit I was able to do to make her life more comfortable. This included but was not limited to helping improve the mobility in her neck and thorax. This was essential in the first steps of her treatment to release some of the longer lines of leveraged tension that were keeping the base of her cranium restricted.

I was also able to soften intracranial tensions that at first palpation felt like tight wires clenching through the encephalon. Releasing the tentorium cerebelli especially made a difference as upon my first interaction with this tissue I could only give it about 1 gram of force to help traction some of the tension out of this reciprocal membrane.

Communication with this patient was difficult as she was nonverbal. Most of our communication occurred through the eyes. Other cues involved involuntary wincing or relaxing. One of the most visible ways to witness the positive effects of the treatment was to see the patient light up when she got to my treatment room, especially on days when she was in much apparent pain as I could only perceive she knew that some kind of relief was imminent.

DISCUSSION

PSP can be one of the most challenging conditions for patients and their families. In an article by Moore and Guttman (2014) the goal was to understand the challenges faced by PSP patients and

their families. One of the most common challenges identified is a lack of knowledge of PSP among community workers, physicians, patients, and family members.

PSP is the most common type of atypical parkinsonism. The estimated prevalence is 6.5 individuals per 100,000 (Nath et al, 2001) and the average survival time is just 5 to 7 years (Litvan et al, 1996) The diagnosis of PSP is challenging, especially in the early stages. The PSP Association (United Kingdom) have identified that three quarters of people with PSP are initially misdiagnosed (Online 5) It is possible that misdiagnosis was most often done by family physicians, who would have little awareness of PSP. This impression is supported by the North American organization, CurePSP, where many patients report that their family doctors knew nothing about PSP (Online 6).

This can be a definite obstacle in having these patients receive the care that they need in the matter of timely fashion which is as soon as possible.

For maybe only a few, alternative treatments such as Osteopathic Manual Treatment would be most likely to reach the patient in the late stages where there has already been irreplaceable damage to the brain stem. For most however, treatments such as these would miss them altogether.

It is imperative that information regarding this condition be circulated amongst physicians, particularly those whose patients have experienced some sort of traumatic brain injury.

If indeed, successive trauma can permanently damage the glymphatic system, later resulting in a manifestation of chronic traumatic encephalopathy, then direct meningeal treatment to allow for correction and potential rehabilitation of this system could reduce the amount of unnecessary development of these cases.

If those affected can be educated to monitor their symptoms over a longer time span. They may be more likely to seek Osteopathic Care after mild to severe brain trauma. Early treatment may result in potential benefits such as a delay of the progression of degenerative conditions such as Progressive Supra Nuclear Palsy.

If indeed there may be a correlation between PSP patients and prior history of spinal cord trauma and or brain injury then patients who seek care after such events could be recommended to screen periodically to monitor for early signs of degenerative conditions. Alternatively, we could then also be able to monitor how these conditions progress and subject these patients to forms of therapy that may be able to deter the progression of further deterioration.

As of now, there are few known Osteopathic treatment plans currently used to slow or even halt the progression of neurological disorders. If these plans were to be developed, a noninvasive treatment could be useful for managing diseases like PSP at an early stage.

CONCLUSION

Although there is no evidence to support that Progressive Supra Nuclear Palsy can be reversed. There is enough to consider modalities that help in the lymphatic drainage as a means of helping slow the progression of what is only a terribly debilitating condition.

Studies that focus on the effects of Osteopathic techniques on nuclei and brain glymphatics are needed to further advance our knowledge of whether these techniques can actually be helpful. Even though it is extremely difficult to predict the occurrence of such neurological digressions, it is important for primary health care providers to educate their patients on monitoring any changes they may experience while they age especially after any acute traumas.

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