

APPLICATION OF OSTEOPATHIC CRANIAL MEDICINE FOR ALZHEIMER'S DEMENTIA

The purpose of this literature review is to investigate and propose justification of application of osteopathic cranial manipulative medicine as a non-pharmacological, alternative treatment for Alzheimer's dementia

AUTHORS

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References



THE GLYMPHATIC SYSTEM & ALZHEIMER'S

What is the Glymphatic system?

First described by Iliff et al in 2012, the glymphatic system is a relatively new concept, essentially proposing a lymphatic or drainage system in the brain. Increased accessibility and ability of measuring biomarkers, such as beta-amyloid proteins, in both mice and humans has provided further support for this theory and concept. Given the close relationship between removal of waste products and incidence of neurodegenerative diseases, the glymphatic system has been suggested as key player in the onset of Alzheimer's dementia (AD). Bohr et al (2022) breaks down the flow of CSF into four parts, but the glymphatic system only covers the first three of these parts.

1. After generation from the choroid plexus, CSF influxes into brain tissue from perivascular spaces and pathway, smooth muscle contraction as a result of arterial pulsations, or facilitation by aquaporin 4 water channels (AQP4) found on astrocyte end feet [2,5,7].
2. Once in the parenchyma, interstitial solute movement is encouraged by advection and diffusion. Both movement processes are needed to move an array of solute sizes [2].
3. CSF is then drained from the parenchyma to its expected compartments/arachnoid granulations, while its solutes are collected by meningeal lymphatic vessels [2,4].

The last part that Bohr et al (2022) list involves eventual drainage of solutes removed from CSF by meningeal lymphatic vessels into the body's lymphatic system. Ultimately, the primary function of the glymphatic system is to move solutes and therefore waste products or proteins that have been produced by the brain during wakefulness [2,5].

Glymphatics role in Alzheimer's

The Alzheimer's Association estimates that 6.9 million Americans currently live with an AD diagnosis. This does not include those who have yet received a formal diagnosis or the many living with mild cognitive impairment (MCI), which is known to precede AD [6]. The glymphatic system plays a key role in reducing AD risk in its ability to remove proteins such as tau proteins and beta-amyloid proteins, which are known to accumulate in those with AD. The following factors may create a dysfunctional glymphatic system and thereby advance AD pathology.

- Increased age: AD is most prevalent in adults 65 years and older [1].
- Sleep disturbances or lack of sleep: The glymphatic system is active during sleep or sleep-like states [5].
- Decreased polarization of AQP4 channels: Decreased polarization of AQP4 channels is indicative of decreased function and transport of fluid into brain tissue. Both post-mortem studies of those with AD and knockout of AQP4 in mice have further supported decreased AQP4 activity as a key player in protein accumulation [5,11].

OSTEOPATHIC CRANIAL MEDICINE

Osteopathic cranial manipulation/medicine (OCM) is subtype of osteopathic medicine. Credit of creation is given to Dr. William Sutherland sometime in the early 20th century after he compared the cranium to fish gills and respiration. This then developed into reformation of principles initially presented by osteopathic medicine founder, A.T. Still. The proposed principles are as follows:

- There is inherent motility of the brain and spinal cord.
- There is fluctuation of the cerebrospinal fluid.
- There is mobility of the intracranial and intraspinal membrane.
- There is articular mobility of the cranial bones.
- There is involuntary mobility of the sacrum between the ilia.
- This is interdependent with the motion at the sphenobasilar synchondrosis [7].

The culmination of these principles is known as the primary respiratory mechanism (PRM). This concept itself breaks down:

- Primary: directly involving "internal tissue respiration" of the central nervous system [7].
- Respiratory: the physiological function of the interchange of fluids necessary for normal metabolism and biochemistry.
- Mechanism: coordination of parts involved to work in unity with each other.

PRM is the basis for OCM and has largely remained intact since its inception. The ultimate purpose and goal of OCM is to improve structure and function within an array of patients. Very few circumstances exist in which OCM is contraindicated, making it a legitimate alternative for older adults who are unable to receive direct or more aggressive osteopathic treatment.

There are many OCM techniques that an osteopathic physician may use. While a specific technique may be mentioned or referenced in this review, the goal of this project is to propose OCM as a whole as an alternative or adjunctive treatment for those with AD.

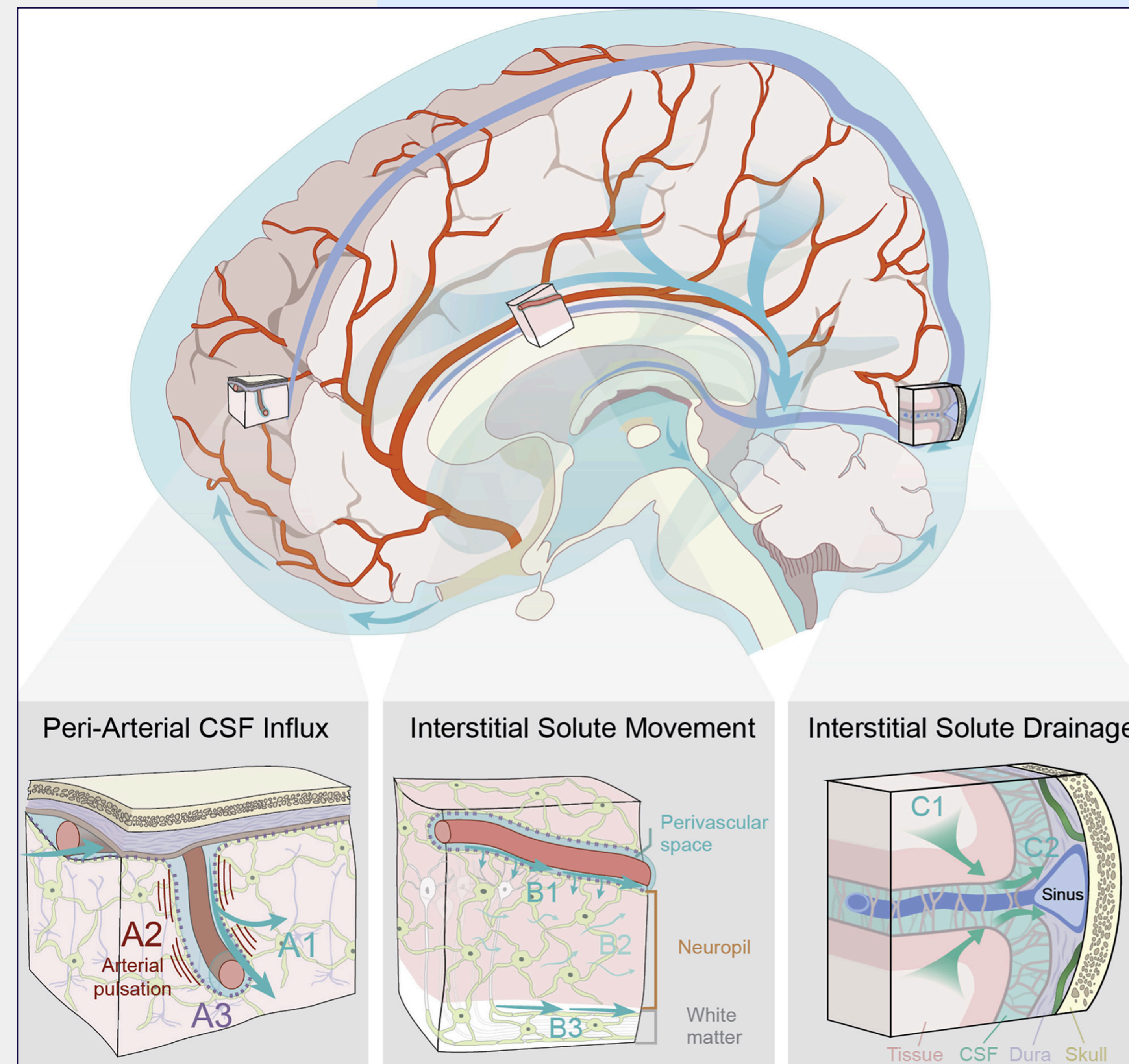


Fig. 1: An updated glymphatic model by Bohr et al 2022. A1-A3 illustrate CSF influx into brain tissue. B1-B3 illustrate the areas over which solute movement occurs. C1-2 illustrate drainage of CSF and the solutes collected from brain tissue [2].

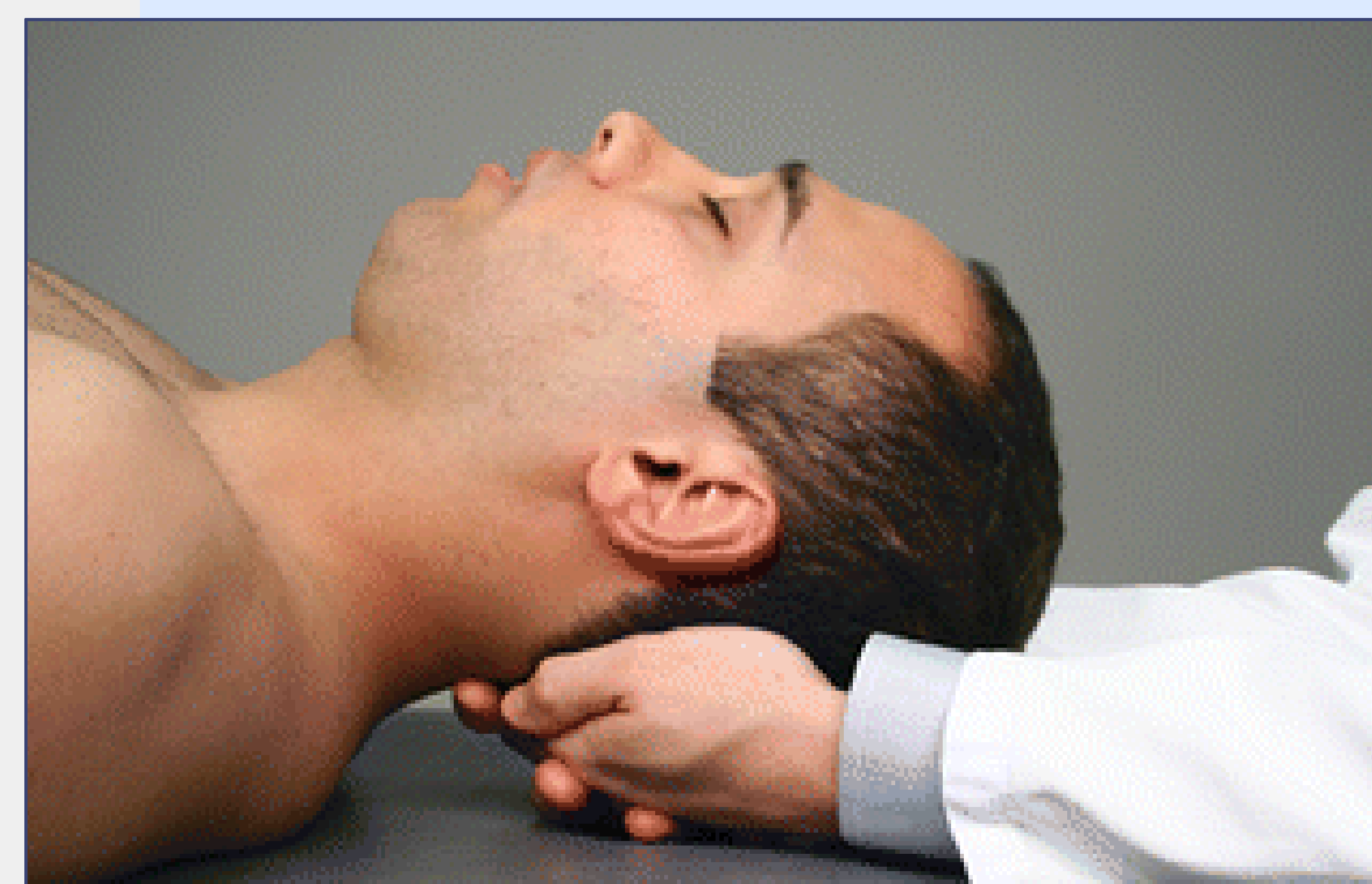


Fig. 2: From Nicholas & Nicholas (2016), an example of an OCM technique called 4th ventricle compression [7].

PROPOSED PREDICTION

We hypothesize that osteopathic cranial manipulation (OCM) will significantly improve glymphatic drainage, demonstrated by enhanced imaging results showing increased cerebrospinal fluid flow and clearance of neurotoxic waste. We propose that this research could establish OCM as a novel, non-invasive approach to mitigating Alzheimer's risk, ultimately contributing to better brain health in aging populations.

JUSTIFICATION FOR PROPOSAL

AD not only affects million of older adults in the U.S. and worldwide, but is trending to increase in incidence in the coming decades. This proposal is relevant to millions of patients and families with an AD diagnosis seeking alternative or adjunctive treatment for their AD diagnosis.

OCM has the potential to benefit those with AD due to it's proposed ability to motivate CSF movement and the glymphatic system.

- PRM explains the basis for how OCM works, specifically "fluctuation of the cerebrospinal fluid" and "motility of intracranial and intraspinal meninges" [9], providing a foundation that OCM would positively impact AD.
- McAree et al (2019) notes that 4th ventricle compression (CV4) is evaluated for possible use as preventative treatment for patients with a family history of AD, in order to maintain the integrity of the blood brain barrier which is broken down in the progression of AD (Fig 2) [6].
- Guo et al (2023) states that "enhancing meningeal lymphatic drainage of CSF macromolecules in aged mice by local injection of recombinant VEGF-C reduces A β deposition and improves cognitive function" [4]. This is relevant because multiple OCM techniques target drainage of the meningeal lymphatics, without the need for injection or invasive procedure.

OCM differs from traditional AD treatments in that it is a non-invasive, non-pharmacological treatment.

- AD disproportionately affects older adults and concerns for polypharmacy is most prevalent in those aged 65 years and older [3,12].
- Those with an AD diagnosis are more likely to be prescribed medications than those without AD, putting them at an even greater risk negatives associated with polypharmacy [3].
- OCM is used for various somatic dysfunctions currently, so patients do not have to undergo AD specific OCM/OMM treatments, which may help decrease stigma felt by those with AD.

CONCLUSION

Use of OCM to try to increase glymphatic flow is a good potential additional treatment for patients with AD, MCI, or that have a family history of Alzheimer's. Various OCM techniques, such as CV4, target the fluctuation of CSF and have been shown to increase CSF movement.

Since glymphatic drainage slows as we age, there is an accumulation of waste products, specifically tau and beta-amyloid, from the brain. This increase in waste products has been linked to the severity of Alzheimer's dementia. Increasing the CSF fluctuation can help improve the removal of these waste products and proteins produced by the brain. This could potentially slow the progression of Alzheimer's. Additionally, since OCM is non-invasive and non-pharmacological it has decreased risk for comorbidities that are present with medications. Future considerations for this topic include a retrospective study to identify if any osteopathic physicians have found results after using OCM to treat patients with AD or MCI. The current research surrounding OCM in application to the glymphatic system is significantly limited.