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CLINICAL HYPOTHESIS

One element of a subluxation complex:

Disruption of articular motion through the intervertebral foramen influencing the IVF, CSF, and neural transmission.

An hypothesis

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Narrative: This report discusses possible factors thought to alter nerve transmission as influenced by segmental mechanical disruption being one of the elements in a Vertebral Subluxation Complex (VSC). In addition to noxious sensory input, this discussion raises the possibility of the following physical modifier under the influence of segmental biomechanical disturbance.

We hypothesise on what potential influence an intersegmental functional fixation may have on vascular and Cerebrospinal Fluid (CSF) circulation due to disturbed neural function within the Intervertebral Foramen (IVF).

As the adjacent lips of articular facets form a part of the IVF margin, it is proposed here that the intersegmental articular fixation element of a VSC has the potential to also limit motion within the foramen, and potentially modify the flow of CSF within the neural sleeves which bathe the spinal nerve roots. We speculate that the effect of the fixation may lead to CSF stasis, or at least reduced CSF circulation within that radicular setting. In turn, that this may effect the spinal nerve root neurons and nerve transmission. Telano & Baker (2022) and Whedon and Glassey (2009) state that CSF '*appears to be particularly prone to stasis due to the relatively high capacitance of the lumbar cistern and lower intrathecal pressures in the distal spinal canal.*'

Indexing terms: Chiropractic; Vertebral Subluxation Complex; Subluxation; IVF; Intervertebral foramen; CSF; Hypothesis.

Editors note: Read this paper along with Pessa's report (Plast Reconstr Surg Glob Open 2022;10:e4126; DOI 10.1097/GOX.0000000000004126) discussed in the Editorial of this issue regarding CSF within neural sheaths throughout the body.

Introduction

'*We hypothesize that stasis of the cerebrospinal fluid (CSF) occurs commonly and is detrimental to health.*' (Whedon & Glassey, 2009)

Historically the significance of the intervertebral foramen in the manual sciences was recognised by Palmer in 1910, and Oakley Smith in 1906. Medically, Swanberg extensively researched this anatomical feature in 1914.

Vertebral dysfunction associated with the subluxation hypothesis includes nerve interference at the intervertebral foramen (IVF). This discussion explores elements that may be involved in such a condition when the dysfunction is a segmental fixation of adjacent vertebral facets.

> *... The equivocal term 'nerve interference' is hardly sufficient to identify changes that may occur, and we should we consider it to be far more complex...'*

As elements of a vertebral subluxation complex, there are a range of mechanisms involved with disruption of vertebral function, particularly segmental fixations with or without displacement. Evidence would suggest that this form of disturbance may include modification of IVF contents, of neuron physiology including nerve root ganglion, and neural transmission of radicular nerves, with the resultant clinical manifestation of clinical signs and symptoms.

This presentation seeks to offer a hypothesis at a cellular level as to the possible contributing influence through a degree of stasis of the CSF which essentially acts as a lymphatic system for the central nervous system together with the dural network of lymphatics. (Aspelund et al, 2015; Tumani et al, 2017; Tamura et al, 2020; Giles, 2023b)

The relevance of this hypothesis becomes highly complex when one considers the extensive range of electrolytes and other CSF constituents and the interactions and interdependence between them. Biochemical considerations in this review are many and complex. It is beyond the scope and intent to analyse all of them at this time.

Although not associated with subluxations or manipulation, awareness of the potential neurological role of the IVF was noted by Sunderland almost five decades ago when he opined '*The relationship of the meninges internally to the nerve roots, posterior root ganglion, and spinal nerve, and externally to the wall of the intervertebral foramen, has been investigated. The neural structures and their coverings are not attached to the foramen. Only the fourth, fifth, and sixth cervical spinal nerves have a strong attachment to the vertebral column, and this is to the gutter of the vertebral transverse process. The observations have relevance to any local lesion that may fix, deform, or otherwise affect the nerve and nerve roots to the point of interfering with their function. They may also be important to traction injuries of nerve roots.*' (Sunderland, 1974)

Since then, Tanaka et al concluded that their '*... study demonstrated the anatomy of the nerve roots, rootlets, and intervertebral foramina, and may aid in understanding the pathology of cervical radiculopathy. The presence of intradural connections between dorsal nerve roots and the relation between the course of the nerve root and the intervertebral disc may explain the clinical variation of symptoms resulting from-nerve root compression in the cervical spine. To perform cervical foraminotomy for cervical radiculopathy, it is necessary to understand the detailed anatomy of the intervertebral foramina thoroughly*'. (Tanaka et al, 2000)

The pathophysiology presented here is derived from the more severe types of injuries to peripheral nerve tissue to that which may be incurred by extracellular fluid (CSF) changes in the IVF, or that may affect the intraforaminal nerve root through facet functional fixation.

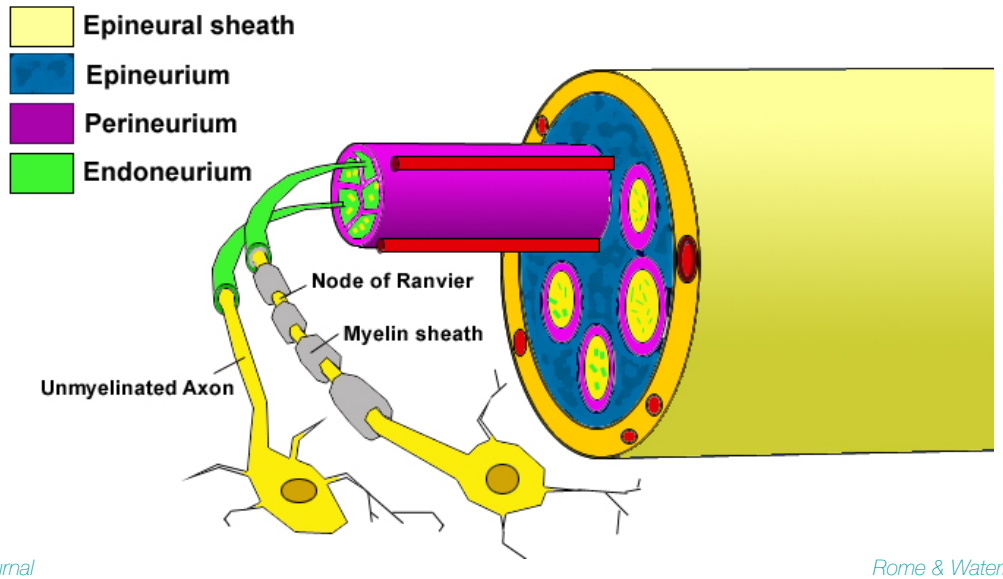


Fig 1: Nerve fibre, showing vasa nervorum and nervi nervorum (After Bates, Peripheral Nerve Injury & Repair 2023)

To our knowledge, this is the first published discussion to review factors at a cellular level in relation to a neuron within the IVF regarding CSF, and consequently nerve transmission (except for direct impingement) being a possible element of a vertebral subluxation complex (VSC). (Whedon & Glassey, 2009)

Vertebral subluxation complex (VSC)

For purposes of this discussion, we offer the following definition of a VSC under which this hypothesis is focussed. (Giles, 1992; Panzer 2005; Baba,2021) The considerations presented here as well as the these three key components of displacement, dysfunction and neural disturbance surely qualifies the VSC as a complex, and may be defined as

> An articular dysfunction with or without displacement, typically but not limited to the spine and pelvis and characterised by anatomical and physiological modifications with associated neurophysiological signs and symptoms which may be addressed by a specific manual or instrument assisted segmental adjustment.

It then follows that addressing this segmental articular dysfunctional lesion demands a specific modification to restore those three elements as far as possible. This restitution or intervention is referred to as an adjustment which may be defined as

> The physical application of a highly developed finely tuned advanced form of manual or instrument assisted intervention directed to restore specific anatomical, functional and neurophysiological elements of an articular subluxation in order to ameliorate associated signs, symptoms and altered physiology.

Vertebral facet dysfunction

An arc of the outer edge of intervertebral facets form part of the perimeter of the IVF. This allows a degree of motion within the IVF. We hypothesise that a loss motion, excessive, or aberrant motion may affect the primary structures within the IVF by way of modification of functional and neurosensory pathophysiology. We suggest that a segmental fixation may preface a stasis of CSF motion, or at least modify CSF flow and the nerve root. (Budgell B, 2005)

Degeneration of the intervertebral disc also contributes further to alter the dimensions of the IVF with the potential to compromise the spinal nerve roots. (Boyle et al, 1998; Sohn et al, 2004; Hasegawa et al, 1995)

Facet gliding

Given that gliding motion of physiologically functioning articular facets may influence motion within the IVF, it is hypothesised that increased, excessive (hypermobile), or reduced motion (hypomobile), may also contribute to modified CSF flow within the IVF. Further, that these changes register with the sensory nervous system. Madalina et al (2012) recognise the proximity of the zygapophysis joint to the posterior nerve root.

Neural stretching

Another characteristic of peripheral nerve tissue itself is inter-fascicular gliding. Given the normal articular gliding with postural flexion, lateral flexion and extension, one would expect a degree of physiological stretching of the inter-fascicular epineurium to take place. With facet fixation, the articular and nerve gliding may be reduced, although the physiological effect this has on neuron physiology is not known. (Millesi et al, 1990; Afshar & Tabrizi, 2020; Beltran et al, 2015; Mountzouri et al, 2012)

Tian et al note that the subtle stretching of a neuron under '*mechanical loading*' may result in '*in microstructural changes in neural tissue and further leading to abnormal electrophysiological function*' and that '*that the increasing axial strain induces a decreased membrane action potential*

and a more frequent neuronal firing'. (Athamneh et al, 2017; Tian et al, 201; (De Vincentiis et al, 2020)

De Vincentiis et al (2020) showed that even extremely low intracellular forces of motion can influence axon growth by '*by inducing a drastic cytoskeleton remodelling, in response to signalling molecules.*' (Falconieri et al, 2023) It is suggested that facet displacement and disc compression may provide further sources of neuron disturbance to nerve roots within the IVF.

Facet function

A vertebral fixation may exist with the facet surfaces remaining in their neutral position. Or if slightly displaced, must also be fixated to remain in that state. (Cramer et al, 2006) It is this form of functional blockage (dysfunction) and its effect in the IVF that is discussed here.

However, as dysfunction may occur with or without displacement, it may be the combination of the displacement and dysfunction that seems to be more common clinically. (Song, 2003)

Articular functional fixation or functional blocking is a noted phenomenon. (Tuling & Huss, 1999; Gibbons & Tehan, 2001; Goel et al, 2011; Reed et al, 2013; Rome & Waterhouse, 2021) The effect of this on CSF flow and the significance of it has yet to be examined at the cellular level.

Altered vertebral function may be firm, partial, or an aberrant motion. Further, functional fixation is considered here as the primary form of motion pathophysiology. Indications of fixation may include segmental: tenderness, palpable structural changes, intrinsic and postural muscle weakness or hypertonicity, nerve root impingement, displacement, neurological (somatoautonomic, somatosensory, somato-vascular, or radiculopathy). These are the prime elements in a clinical setting in identifying contributors to symptoms. (Henderson et al, 2007; Haavik et al, 2021; Rome & Waterhouse, 2020)

As an indication of a somato-neurological functional association, preliminary morphological evidence that vertebral hypomobility induces synaptic plasticity was noted by Bakkum et al when they stated '*... chronic vertebral hypomobility at L4 through to L6 in the rat affects synaptic density and morphology in the superficial dorsal horn of the L2 spinal cord level.*' (Bakkum et al, 2007) They also note '*vertebral hypomobility as a cause of morphological changes in dorsal horn synapses.*'

Mechanical factors

In cases where the subluxation involves actual displacement resulting in altered IVF dimensions, segmental hypermobility appears to attract far more discussion in the literature than loss of mobility. However, there remains significant attention placed on the loss of vertebral motion. Emphasis is placed here on the effect of this as the facet fixation forms a part of the border of the intervertebral foramen.

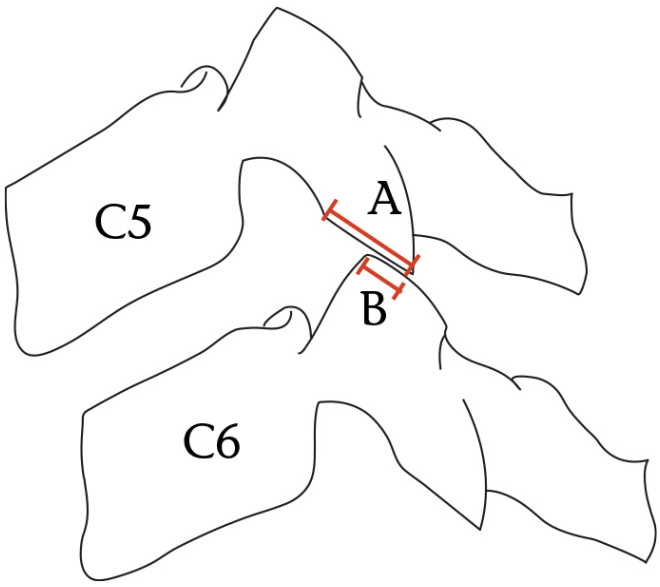


Fig 2a: Altered dimensions if the IVF with facet translation. (Schleicher et al, 2018)

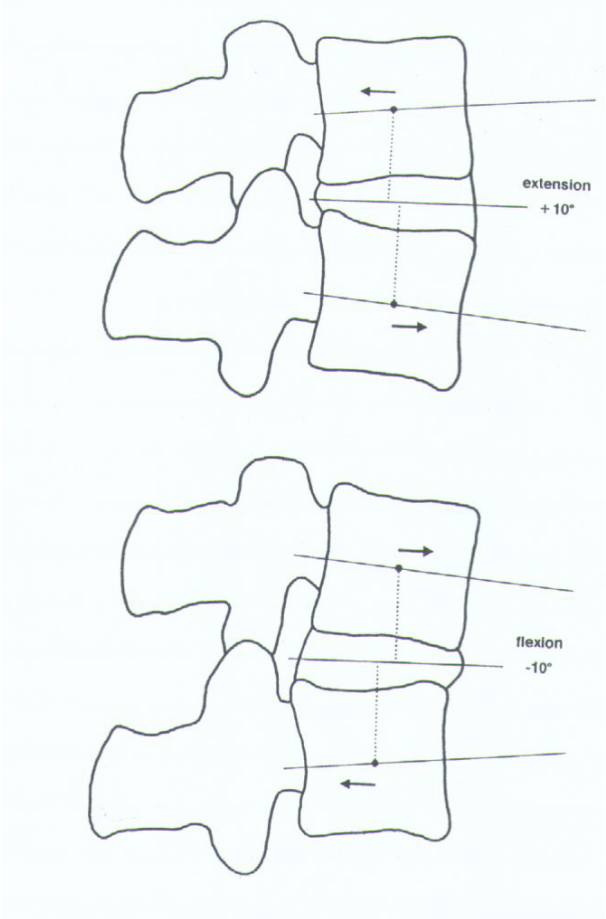


Fig 2b: Altered dimensions of the IVF with sagittal motion (Frobin et al, 1997)

Altered dimensions if the IVF with facet translation. (Schleicher et al, 2018) (Figures 2a, 2b) demonstrates the potential alteration in IVF dimensions without degenerative disc compression. If a vertebra was functionally fixated in these positions consideration of the long-term effect may be made. (Rühli et al, 2006)

The influence of disc integrity and lumbar facet motion have also been discussed by Fujiwara et al. (2001)

Anatomical considerations and factors which may affect the IVF

The clinical picture is established by the imposition of a biomechanically disturbed vertebral segment, this is the irritant disruption that may be identified as a dysfunctional fixation or one form of a VSC. (Gatterman, 2005; Leach, 1994; Haldeman, 1996; Yockum & Rowe, 1996)

Using CSF biomarkers, Tsitsopoulos et al (2012) found that damage to glial cells and axons in cervical spondylotic myelopathy and may reflect neurological status. Biomarkers may be a method of monitoring neural disturbances in the IVF. Other radiological displacements of vertebra have been noted by Thiyagaraian on his website *https://www.slideshare.net/drthiyaga/roentgenometrics*. (2012)

Table 1: Considerations of Anatomical and Physiological Components of Nerve Injury (Extrapolated from Bates, 2023) Summary of anatomic, pathophysiologic, and pathomechanal/functional considerations of the findings to be considered as having a possible influence on motion alterations through the IVF.

Anatomically (Gilchrist et al, 2002)

- Dorsal root ganglia (Yoshizawa et al, 1991) (Sugawara et al, 1996)
- IVF bathes the dural sleeve in CSF (Borg et al, 2022) (Giles 2023, p44) (Figures 2 & 3)

- IVF contents (Cramer et al, 2002) (Arslan et al, 2017) (DiSabato et al, 2016))Figure 4)
- Nerve root IVF occupancy (degree of) (Figures 3) (DiSabato et al, 2016)

Fig 3a: Dural sleeve

https://clinicalgate.com/spinal-cord-and-nerve-roots/

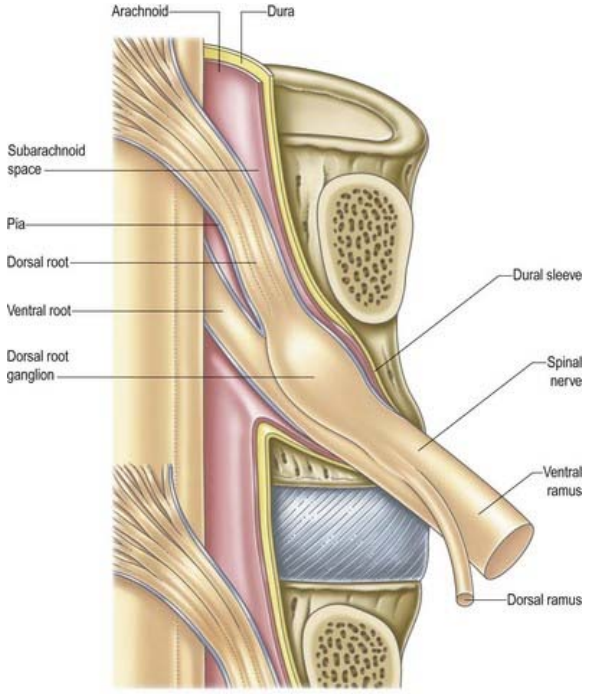
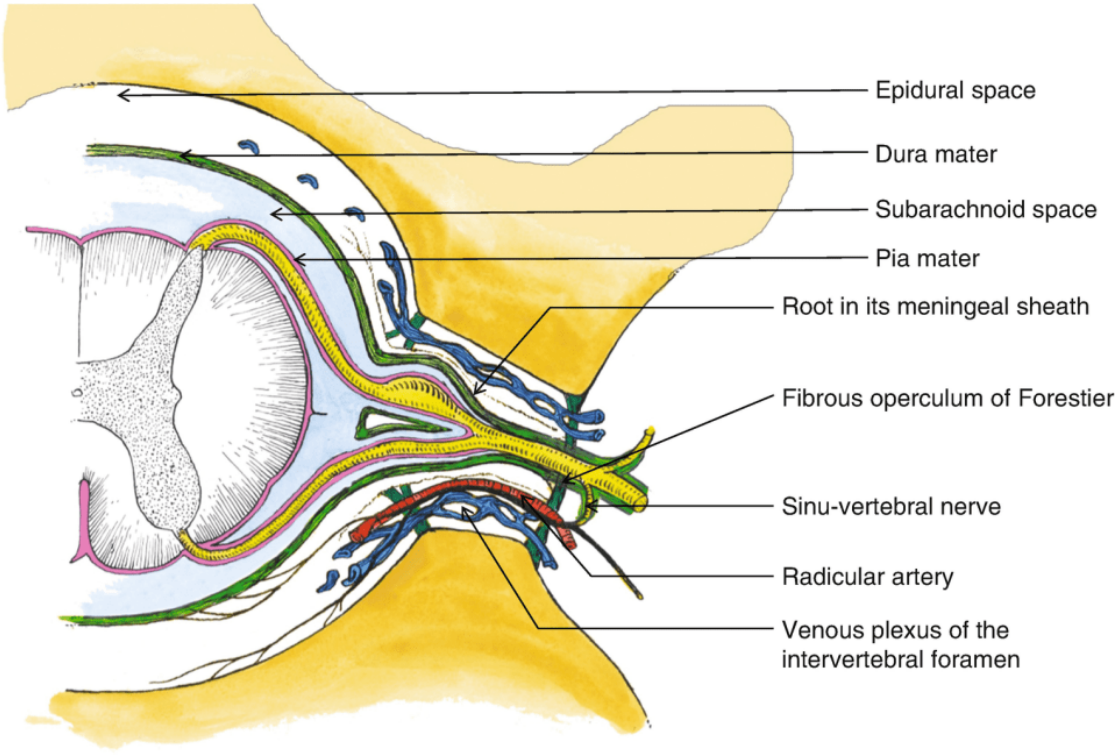


Fig 3b: Dural sleeve and IVF contents. Nerve roots in their meningeal sheath in the intervertebral foramen, schematic drawing. Monnet JP. https://musculoskeletalkey.com/of-the-spinal-meninges/



Stretching injury

- 8% elongation will diminish nerve's microcirculation
- 15% elongation will disrupt axons
- compression/crush
    - fibres are deformed
        - local ischemia
        - increased vascular permeability
    - endoneurial oedema leads to poor axonal transport and nerve dysfunction
    - fibroblasts invade if compression persists
        - scar impairs fascicular gliding
    - chronic compression leads to Schwann cell proliferation and apoptosis
    - 30mm Hg can cause paresthesias
        - increased latencies
    - 60 mm Hg can cause complete block of conduction

Pathophysiology

- presynaptic terminal & depolarization
    - electrical impulse transmitted to other neurons or effector organs at presynaptic terminal
    - resting potential established from an unequal distribution of ions on either side of the neuron membrane (lipid bilayer)
    - action potential transmitted by depolarization of resting potential
    - caused by influx of Na across membrane through three types of Na channels
        - voltage gate channels
        - mechanically gated channels
        - chemical-transmitter gated channels
- Indications of signs and symptoms. (Hourigan & Bassett, 1989)

Functional pathophysiology

- Facet fixation (non-surgical) – functional fixation (Reed et al, 2013) (Rome & Waterhouse 2021)
- Facet subluxation (Tuling & Hsu, 1999) (Baba , 2021
- Functional condition of the segment -dysfunction. (Reed et al, 2014)

Circulation

- The CSF is a form of circulation. (Whedon & Glassey, 2009) cite (Muhle, et al 1998) (Nakamura et al, 1997) (Yildiz et al, 2022)
- pH may be affected by CSF stasis over time.
- extrinsic vessels
    - run in loose connective tissue surrounding nerve trunk
- intrinsic vessels
    - plexes lie in epineurium, perineurium, and endoneurium

Nerve structure (Figure 1)

- epineural sheath
  - surrounds peripheral nerve
- epineurium
  - surrounds a group of fascicles to form peripheral nerve
  - functions to cushion fascicles against external pressure
- perineurium
  - connective tissue covering individual fascicles
  - primary source of tensile strength and elasticity of a peripheral nerve
  - provides extension of the blood-brain barrier
  - provides a connective tissue sheath around each nerve fascicle
- fascicles
  - a group of axons and surrounding endoneurium
- endoneurium
  - loose fibrous tissue covering axons
  - participates in the formation of Schwann cell tube
- myelin
  - made by Schwann cells
  - insulates axons to increase conduction velocity
    - conduction occurs at nodes of Ranvier
- neuron cell
  - cell body - the metabolic centre that makes up < 10% of cell mass
  - axon - primary conducting vehicle
  - dendrites - thin branching processes that receive input from surrounding nerve cells

- Innervation of facet capsule, (Kallakuri, 2012)
- Nerve root irritation (Aldrete, 2003)
- Radicular compromise (Anaya et al, 2021)
- Radicular vulnerability (Manchikanti, 2015) . (Prats-Galino et al, 2012)

Pathology

- Articular inflammation – cartilage (Jackson 1966, p122,124) (Giles, 2023)
- Radiculitis Inflammatory response in nerve root (Christensen & Buswell, 2008)
- Consideration of the condition of the intervertebral disc and facets (Bashkuev et al, 2020)
- Inflammation of facet capsule localised oedema (Perolat et al, 2018)
- Joint degeneration – degree, exostosis (Perolat et al, 2018)
- Radiculitis Inflammatory response in nerve root (Christensen & Buswell, 2008)

Pathoanatomy - biomechanical

- Atlantoaxial "overhang" sign, (Thiyagaraian, 2012)

- Atlas malposition (Thiyagaraian, 2012)
- Barge's "e" space, -.(Thiyagaraian, 2012)
- Cervical toggle analysis (Thiyagaraian, 2012)
- Cervical, thoracic, and lumbar endplate lines, (Thiyagaraian, 2012)
    - Compression of nerve root from disc bulge, osteophyte formation (Dahlin, 1992)
- Coupled spinal motion sign (Thiyagaraian, 2012)
    - Disc may bulge into the IVF reducing patency of IVF
- Facet fat pads – enlarged, periarticular. (Giles & Taylor, 1991) (Taylor & McCormick, 1991) (Giles, 2000)
- Hadley's curve (Lumbar) (Thiyagaraian, 2012)
- Intervertebral mechanical fixation or 'blockage' - one of the physical components of a VSC. (Gatterman, p390)
- Joint degeneration – degree, exostosis
- Neurophysiological lesion (Taylor, 2023)
- Proximity of facet and posterior-inferior margin of the vertebral body on displacement (Rydevik et al, 1984)
    - Segmental displacement – radicular compromise – depending on the degree of displacement (Munalomi & Das, 2023)
- Segmental disruption, displacement (Thiyagarajan. 2012) S.
- Somatic dysfunction/fixation (Henderson et al, 2007)
- State of certain postural muscles. hypertonicity
- State of intrinsic muscles. (Bogduk, 2016)
- Subluxation (Gatterman, 2005) (Leach, 1994) (Eriksen, 2004) (Sharpe, 2021) (Panzer, 2005) (Munalomi & Das, 2023)
- Van Akkerveeken's measurement of lumbar instability. (Thiyagaraian, 2012)
- Vertebral fixation/mechanical blockage/functional fixation (Goel & Shah, 2011) (Reed, et al, 2013)

Redress

- Effect of mobilising on IVF patency. (Song et al, 2003, 2006; Afzal et al, 2019; Haavik et al, 2021a; We et al, 2022; Taylor, 2022; Yang et al, 2016)

Together with a patient's occupation and hobbies, the degree of the severity of the biomechanical disruption as well as its duration would be two of the key factors in the influence upon these disturbed vertebral segments. (DiSabato et al, 2016) Lundborg and Dahlin (1996) discussed the pathophysiology on microanatomy on peripheral nerve injuries and the long-term effect of minor compression (<20mm/Hg). They state '*The clinical stages of nerve compression lesions can be related to changes in intraneural microcirculation and nerve fibre structure; alterations in vascular permeability, with subsequent formation of oedema and deterioration of nerve function observed in experimental studies*.'

In a further study they found that '*Compression of a peripheral nerve can disturb the intraneural transport (axonal transport) of a large variety of substances. This may be followed by morphological and biochemical changes in the nerve cell body*.' (Dahlin and Lundborg, 1990)

Environs of the IVF

The clinical condition of vertebrogenic sciatica attributed to a vertebral fixation with or without displacement may be alleviated by segmental adjustment or manipulation for release of that fixation. This suggests that its aetiology may not be radicular impingement that compromises the nerve root but may have a noxious somatosensory reflex as well. (Gudavalli et al, 2023) This clinical observation suggests that the degree of impingement is not necessarily the only factor, but the neurons in the nerve root may be irritated or compromised by another cause other than mechanical. Farmer and Blum (2002) propose a special manual technique called dural port therapy as a means of influencing the meningeal system of the CNS, including the dural sleeve.

In a recent study of the dural sac, Pick (2022) noted an influence of the lumbosacral meningeal region with pressure applied to the cranium, potentially through changes in CSF pressure. We hypothesise that this may also have an influence on the dural sleeve fluid pressures along the spinal cord. (Figures 2)

In a detailed review, Hodgson (2006) examined a clinical role of the dural attachments in relation to chiropractic spinal care with the *Torque release technique* model. While there are a range of attachments of the dura, the IVF can be one of them, although Hodgson states that this can vary

Cerebrospinal fluid

Cerebrospinal fluid (CSF) is a physical protector of the brain and spinal cord and is essential physiologically. It is mostly contained in '*The cerebrospinal fluid (CSF) space (which) consists of the intra-cerebral ventricles, subarachnoid spaces of the spine and brain (e.g., cisterns and sulci), and the central spinal cord canal. The CSF protects the central nervous system (CNS) in different ways involving metabolic homeostasis, supply of nutrients, functioning as lymphatic system, and regulation of intracranial pressure*.' (Tumani et al, 2017)

This review proposes a hypothesis regarding the effects of CSF stasis in the dural sleeve as it extends into an intervertebral foramen (IVF). In doing so, it raises the issue of possible influence at a neuronal level, and subsequently on neural transmission. During lumbar punctures and spinal anaesthesia blocks, the vulnerability of nerve roots may be noted in that such procedures can influence CSF pressure. (Prats-Galino et al, 2012) This then raises the topic of a possible effect on single neurons within a spinal nerve root in its dural sleeve within the intervertebral foramen. (Prats-Galino et al, 2012; Manchikanti et al, 2011; Steer & Horney, 1968; Yates, 1968)

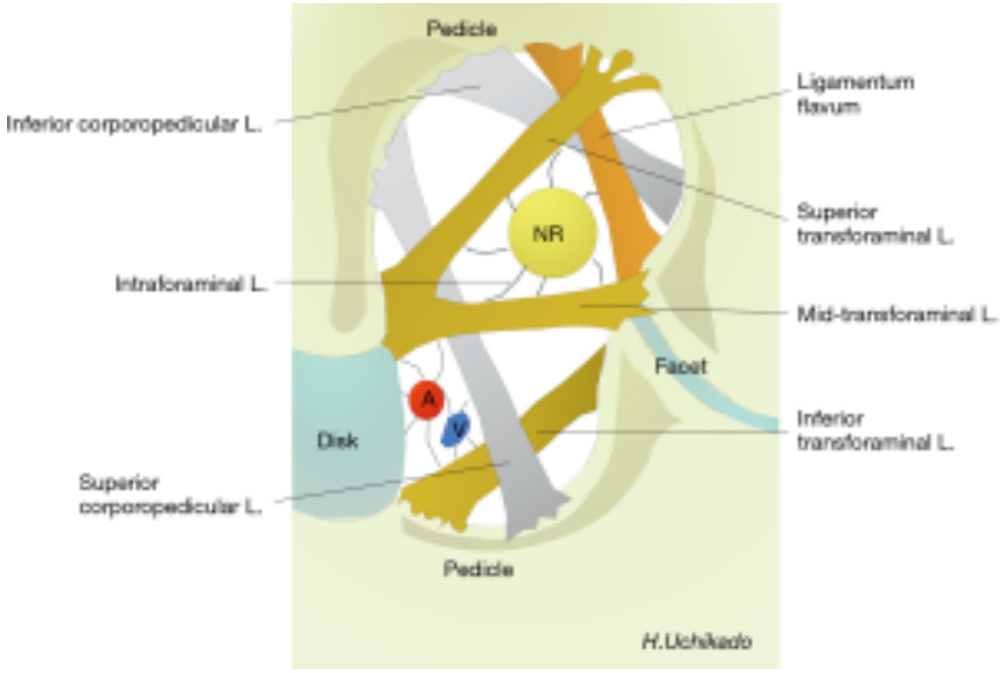
Motion through the vertebral articulations bordering the IVF conceivably provides impetus for ensuring that the spinal wave motion of CSF is maintained to perpetuate the fluid pulse wave circulation in the radicular setting. (Cramer et al, 2002) Not only does this help maintain the integrity of the nerve root but also the dorsal root ganglion in the region. (Nakamura, 1997)

As a more severe example of the possible influence of mechanical irritation and sensitivity, Tsitsopoulos et al found that CSF biomarkers of glial and axonal damage, inflammation, and synaptic changes are altered in symptomatic cervical spondylotic myelopathy (CSM) patients, indicating that axonal injury, astroglial activation, and Aβ dysmetabolism may be present in these individuals. These findings reflect CSM pathophysiology and may aid in prognostication. (Tsitsopoulos, et al, 2021)

The intimate proximity of the intervertebral facet and vulnerability of the nerve root are noted. (Uchikado et al, 2020) However, Cramer et al found that not all IVFs contain transforaminal ligaments which wary in thickness. (Cramer et al, 2002) Min et al concluded that transforaminal ligaments '*may reduce the space available for the spinal nerve root within the IVF. In this circumstance, any compromise of the IVF may impinge on the nerve root*'. (Min et al, 2005) Sioutas

and Kapetanakis (2016) describe the intricate gross anatomy of cervical intervertebral foramina, but do not identify intraforaminal ligaments.

Fig 4: Ligament structure within the IVF. (Uchikado et al (2020) [This schematic does not include the recurrent meningeal nerve, fat pads, or microcirculation of blood and lymph vessels.]



Reduced intersegmental motion, and a fixation in particular, appear to inhibit the normal functions of the CSF. (Whedon & Glassey, 2009) The condition and height of the intervertebral disc (IVD) may also be a determinate factor of influence in the efficacy and patency of the IVF dimensions. It must also have a compressive effect on the facet surface. (Alexander et al, 2023)

Pahlavian et al found that the nerve root and the denticulate ligament in the cervical spine: '*had an important impact on CSF dynamics in terms of velocity field and flow patterns*'. They suggested that a function of the denticulate ligaments was to do with mixing the CSF in a vortical affect. (Pahlavian et al, 2014)

In 2016, Puy et al noted the significance of flow oscillations of CSF and importance of this dynamic flow on its biochemistry. (Puy et al, 2016) The next year Djenoune and Wyart (2017) demonstrated an association between sensory detection of mechanical and chemical (e.g. pH) stimuli from the CSF and modulation of locomotion and posture.

In a reflection of an even wider role of CSF, Djenoune & Wyart (2017) discuss an association with mechanical and chemical stimuli from the CSF and their associations with spinal neural circuits with posture and locomotion. This interpretation is noted in their paper's explanatory title as shining a '*Light on a sensory interface linking the cerebrospinal fluid to motor circuits in vertebrates.*' They stated further that '*the CSF could act on neurons in the brain and the spinal cord via bordering receptor cells. Candidate neurons to enable such modulation are the cerebrospinal fluid-contacting neurons (CSF-cNs) that are located precisely at the interface between the CSF and neuronal circuits*'.

Rosa, Middleton, and Baird have demonstrated the limitations in CSF flow and other pathophysiological and anatomical changes that may occur with subluxation in the suboccipital region. (Rosa, 2016, 2019; Rosa & Baird, 2015; Middleton, 2020 2020, 2021, 2022, 2023)

CSF pulse wave

Whedon and Glassey (2009) cite Muhle et al (1998) who noted that spondylosis may already tend to constrain CSF flow pulse wave. We suggest that spondylosis at the same level as a vertebral fixation may further exaggerate a reduction of CSF flow in the IVF. (Nakamura et al, 1997; Rosa, 2019)

In addition, Whedon and Glassey also note CSF flow appears related to different postures in that the cervical subarachnoid space (SAS) may narrow up to 43% and the dorsal subarachnoid space widening up to 89% in flexion. In extension, the cervical SAS may widen up to 9% and the dorsal SAS may narrow up to 17%. These are thought to be related to sagittal diameter changes in the spinal cord with those postural changes encountered in yoga movements and yoga breathing. (Yildiz et al, 2022) These findings could be related to a principle of an optimal flexible spine, one free of functional restrictions as subluxations.

CSF stasis

The focus here is that of CSF stasis within the Intervertebral canal (IVC) and IVF and its effect on neural physiology, particularly around the nerve root and the dorsal root ganglion at the same level. As one potential significant factor, this essentially introduces the effect of hypoxia (Guo et al, 2018) and CSF ischemic changes. (Yoshizawa et al, 1991; Giles & Kaveri, 1990)

Through extensive MRI studies, Rosa and Baird note that '*Misalignments of C0-C1 , C1-C2 brought on by head and neck trauma can manifest as…neural compromise…(and) may contribute to CSF flow obstruction*'. (2015, p48; Rosa, 2019)

pH

While extracellular and intracellular pH may vary, we hypothesise that with IVF stasis of these fluids and CSF may become further factors of influence with the nerve root neurons and consequently impulse transmission and expression. (Wu & Fry 1998; Ruffin et al, 2014)

Hypoxia

The vulnerability of the radicular neural structures to compression has been recognised in relation to hypoxia. (Rydevik, 1992; Sugawara et al, 1996; Lim et al, 2015) (Hernandez-Gerez et al, 2019)

Mukandala et al (2016) note a neuronal response '*to hypoxia include synaptic signalling decreases usually as a result of anerobic metabolism changes whilst chronic hypoxia may give rise to more severe perturbations of synaptic transmission and the activation of transcription factors that regulate oxygen homeostasis.*'

They and others, note the complex actions and responses of neurons under hypoxic conditions. However, their studies primarily are related to brain neurons and glial cells. It may be possible to include the dorsal root ganglion (DRG) and nerve root itself as an extension of the central nervous system due to their anatomical association through the dural sleeve. (Steer & Horney, 1968)

Micro-impingement from increased hydrostatic pressure

While hypothetical under this model at this stage, micro-impingement would influence ionic exchanges through the cell membrane.

Primary biomechanical impingement from bulging discs would be responsible for changes in circulation of both the major foraminal vascular structures, arterioles, venules, as well as microvascular lymphatic and blood vessels in the IVF. (Tamura et al, 2020) This may also have the

effect of reducing CSF flow with a further influence on the nerve root. (Rydevik, 1992; Nishida et al, 2015) There is also the ultimate consideration of demyelination and fibrosis of spinal convergent neurones under chronic compression. (Boulu & Benoist, 1996)

Further, a vulnerable neural structure within the IVF is the DRG. Sugawara et al (1996) and others noted that the '*Dorsal root ganglia are highly sensitive to mechanical compression and hypoxia and closely related to abnormal sensations and pain in radiculopathy*.' (Gladman et al, 2010; Yoshizawa, 1991)

Earlier, Rydevik et al (1984) noted that in nerve root impingement '*The functional changes induced by compression can be caused by mechanical nerve fibre deformation but also may be a consequence of changes in nerve root microcirculation, leading to ischemia and formation of intra-neural oedema*'.

Indicative of the sensitivity, Sizer et al stated that nerve root pain '*can emerge from tension events in the dura mater*'. They noted that '*This compression can result in chemical and mechanical consequences imposed on the nervous tissue within the spinal canal, lateral recess, intervertebral foramina, and extra-foraminal regions*'. (Sizer et al. 2002; Garfin et al, 1991, 1995)

The possibility and degree of micro-compromise in mm/Hg has yet to be ascertained. However, '*Compression alters nerve root conduction and compromises the nutritional support of spinal nerve roots (through intrinsic and extrinsic vascularity and cerebral spinal fluid percolation). Mechanical forces can lead to intra-neural damage and functional changes in nerve roots. Chemical and metabolic effects can create an inflammatory response*'. (Garfin et al, 1995) We suggest that duration of such pressure may also be a significant factor.

While some of the instances cited relate to more extreme impingements, we use these as examples for the VSC situation, given the lack examples and difficulty in obtaining evidence of VSC nerve root compromise in humans (Sugawara et al, 1996) Research is needed to determine the point (mm/Hg) at which pressure has a deleterious effect.

Vascular circulation

In 1975 Drum opined that venous blood flow in the spinal complex was largely dependent on vertebral motor unit motion as it lacked the propulsion assistance of muscular contractions and relaxation. He raised the possibility that vertebral fixations may contribute to pathohemodynamics where impeded venous flow is a form of vascular congestion. The effects of this at the cellular and ionic levels are two of a number of factors in a VSC considered here.

In 1988 Lundborg stated '*Peripheral nerve trunks are well-vascularised structures where a well-developed collateral system may compensate for local vascular damage. Interference with intraneural blood flow is reflected rapidly in disturbances in nerve function. In compression lesions and nerve entrapments, the microvascular factor plays an important pathophysiologic role for development of symptoms. Although endoneurial capillaries normally constitute a BNB helping to optimise endoneurial environment, damage to the vessels may induce a miniature closed compartment syndrome by increasing the permeability, thereby contributing to increased endoneurial fluid pressure and development of an intrafascicular oedema. Surgeons, performing intraneural dissections, should be aware of the potential risks associated with intraneural bleedings, oedema, and intraneural fibrosis*'. (BNB = blood nerve barrier)

While Lundborg's observations relate to more severe vascular damage, they do reflect the type of effects that may be possible. A further goal would be to determine at what level neurons and microcirculation within the IVF are pressure sensitive under subluxations.

Although addressing the spinal cord rather than a spinal root specifically, Ikawa et al (2005) note an ectopic firing may be caused by venous stasis resulting in neurogenic intermittent

claudication. This may be a further factor in disturbance in neural impulse transmission within a spinal nerve root with due consideration to the degree and duration of stasis.

Research by Gao et al suggests that restoration of microcirculation is vital after compression '*Compared with the peripheral nerve, the arterial and venous networks of the spinal nerve root are not abundant, explaining why the spinal nerve root does not tolerate pressure well*'. They also note that '*Damaged nerve roots are connected to corresponding dorsal root ganglion, resulting in ganglion dysfunction. Blood supply at the spinal nerve root arrives from the proximal end of the spinal artery, and from the distal end of the radicular arteries of intervertebral foramina. The two blood-supply systems anastomose a third of the way from the distal end of the nerve root. The vascular density at the anastomotic site is low*'. (Gao et al, 2013)

Yoshizawa (1991) explains the effects of impingement with both direct and indirect CSF and vascular disturbances as factors related to DRG and radicular symptoms.

Using rat subjects Igarashi et al (2005) noted further signs such as endoneurial oedema, DRG ischemia, increased endoneurial fluid pressure, neuronal ischemia and sensory dysfunction.

A potential for changes at a gross level of the intervertebral foramen is discussed by Giles and Kaveri regarding canal stenosis and vascular stasis. This also provides a possible rationale for neuronal changes at a cellular level. (Giles & Kaveri, 1990)

It has also been noted that restoration of a normal cervical lordosis by correction of a cervical hypolordosis improves vertebral artery haemodynamics. Again, there would be an influence upon the intervertebral facet functions and IVF comportments. (Katz et al, 2019)

Hydrostatic pressure at a neuronal level

Indicative of the delicate sensitivity of the IVF vascular structures, a range of studies suggest that relative minor disturbances may interfere with the structures therein.

Using retinal ganglion cells Agar et al (2000, 2006) stated that in acute glaucoma '*… pressure alone may act as a stimulus for apoptosis in neuronal cell cultures. This raises the possibility of a more direct relationship at the cellular level between pressure and neuronal loss*'. Similarly Wann et al, (1979) concluded that:

- High hydrostatic pressure causes reversible depolarisation and a reversible increase in the input conductance of quiescent Helix neurons
- High hydrostatic pressure reduces both excitatory and inhibitory synaptic transmission by reducing the amplitude of the postsynaptic events
- Hydrostatic pressure can alter rhythmically firing action potential activity in a variety of ways depending on the cell type and the temperature
- Hydrostatic pressure increases the duration of the action potential, by slowing both the peak depolarisation and repolarisation rate.

Giles and Kalveri studied stenosis of the IVF and its effect on stasis of vascular circulation, blood vascular and lymphatics, and notably venous stasis in the IVF. In a separate paper, Berthelot et al emphasised that compression is not '*mandatory to induce root/nerve suffering, since root/nerve adherences in two locations can impair blood flow in vasa-nervorum through root/nerve stretching*.' (Giles & Kaveri, 1990; Giles 2000; Berthelot et al, 2018, 2022)

Inflammatory-neurochemical-metabolic response

DiSabato et al acknowledge the multiple neurochemicals involved in neural inflammation, they state: '*Aspects of neuro-inflammation vary within the context of disease, injury, infection, or stress. The context, course, and duration of these inflammatory responses are all critical aspects in the understanding of these processes and their corresponding physiological, biochemical, and*

behavioural consequences. Microglia, innate immune cells of the CNS, play key roles in mediating these neuro-inflammatory responses. Because the connotation of neuro-inflammation is inherently negative and maladaptive, the majority of research focus is on the pathological aspects of neuro-inflammation. There are, however, several degrees of neuro-inflammatory responses, some of which are positive'. (Di Sabato et al, 2016)

Mukandania et al (2016) also present a comprehensive discussion regarding the intricate balance of some of the ions and electrolytes, inflammation, cellular oedema, synaptic signalling, Krebs cycle, glutamate spillover into synaptic regions, and proteins membrane depolarisation. These aspects contribute to the intricate balance necessary for homeostatic neuron physiology. (Nieber, 1999; Calabrese & Duna, 1995)

Further, there are numerous ions, cations, proteins, hormones (ADH), mononuclear cells, immune cells, CD4 T cells, glucose, immunoglobulins, albumen, histamine, and lipids, all of which may be classified as examples of biochemicals in CSF which inter-react with the cell membranes. They are under the influence of hydrostatic pressure which may affect electrolyte transport across those cell membranes. Through the ion channels under an altered CSF state of stasis, especially ADP, O2, CO2, Ca+, HCO3-, and Cl may be affected. Then there is the potential effect of Na+ and K+ transfers have on the pH balance of CSF, plus the influence of the Krebs cycle (citric acid cycle). (Nattie, 1983; Purves et al, 2001; Alberts et al, 2002; Trushina et al, 2013; Seifter, 2019)

In consideration of the duration factor Kleine et al (1994) conducted '*highly sensitive differentiation of non-inflammatory from subacute-chronically inflammatory forms of radicular syndromes*'. They noted extensive constituents in CSF obtained from radicular sites in an inflammatory condition.

In line with the studies by Ingber and others on the tensegrity property of cells, mechanical forces can have an influence upon the cytoskeleton, metabolism, signal transduction as well as cell behaviour. If stasis or other changes in CSF hydrostatic pressure are factors, it may be sufficient to induce abnormal ionic imbalances which influence nerve transmission impulses. These cellular aspects may be influenced by biomechanical displacement factors in some VSCs involving mechanotransduction and mechano-chemistry. (Ingber, I & II, 2003; Ingber et al, 2014)

As highlighted by the Ingber studies the biocomplexity of cellular membrane and molecular interactions is extensive. They note that '*the cytoskeleton also orients much of the cell's metabolic and signal transduction machinery and that mechanical distortion of cells and the cytoskeleton through cell surface integrin receptors can profoundly affect cell behaviour', and '...covers how combined use of tensegrity and solid-state mechano-chemistry by cells may mediate mechanotransduction and facilitate integration of chemical and physical signals that are responsible for control of cell behaviour* ...' (Ingber II, 2003)

Degenerative change of the intervertebral facet

One section of the posterior margin of an intervertebral facet borders a section of the IVF bilaterally. Inflammation of the facet particularly involving that lip section may also influence structures, particularly the capsule and ligaments of the IVF. (Jackson, 1966 pp 51-76)

It is suggested that the inclusion of the rim of the facet may have a notable influence on the integrity of the IVF. '*The results from all of these investigations show that as soon as the structural integrity of facet cartilage is violated, its mechanical properties also become weakened and the response of the cartilage matrix to compression is further modified, which can change the mechanical environment of the chondrocytes and the mechanical response of these cells as well*'. (Jaumard, 2011)

Earlier Jackson had noted the hypomobility of the facet. She stated '*Immobilisation of joints or functional inactivity results in stasis of circulation and is a common cause of post-traumatic joint stiffness. A small amount of movement in injured joints rather than complete immobilisation reduces the inflammation by mobilising or dispersing the tissue breakdown products …'*. (Jackson, 1966 p 121

A number of factors at the neuronal level may be influenced by disturbed environs of the IVF These factors include:

A single neuron may be affected by altered intracellular pressure:

- Axoplasmic transport
- Channel blockers
- Increased extracellular fluid pressure
- Inflammatory response
- Ions, glucose and other metabolites
- Macromolecules
- Membrane potential
- Neuronal polarity (Takano et al,2015, 2019)
- Parenchyma
- Permeability
- Striatal neuron

Impulse effects::

- Action potential*
- Current
- Neurotransmitters (Nieber, 1999)
- Synaptic transmission

*Action potential. Seidl et al (2014) demonstrate that impulse velocity may not only vary but may be modified at a neuronal level.

Inflammatory factors (neuroinflammation) radiculitis:

- Cytokines
- Chemokines
- Reactive oxygen species
- Secondary messengers
- Dolor (pain)
- Rubor (redness)
- Tumor (swelling)
- Functio faesa (loss of function)

Mukandala et al (2016) note that under hypoxia in the central nervous system, synaptic signalling decreases as an attempt to adapt to the anaerobic metabolism. This also activates Na+ and K+ ion channels and glutamate transporters which inhibit neuronal and glial cells leading to an influx of water resulting in oedema. They denote a raft of other biochemical changes effected by a hypoxic environment including a tendency to inhibit the Krebs cycle.

- Adenosine triphosphate (ATP)

- Altered neural conduction
- Donnan's equilibrium
- Electrolyte imbalance - especially Na, K, P, Ca+ HCO.
- Ischemia (with foraminal impingement)
- Membrane polarisation/potential (Nieber, 1999; Calabrese et al, 1995)
- Neuromodulators
- Neurotransmitters
- Oxidative stress
- Oxygen homeostasis
- Sodium pump
- Sodium/potassium balance

Extracellular factors with potential to influence neuronal changes

- Altered membrane potential/ionic exchange. Orchardson and Peacock (1994) noted the significance of the sodium membrane channels in controlling neve excitability. This could be increased by lower extracellular calcium and hydrogen ions.
- Altered metabolism
- Axonal transport
- Axoplasmic flow
- Build-up of cellular waster products
- Cellular integrity – altered neural transmission.
- Changes of intracellular fluid
- Colloidal osmotic pressure altered
- Hypoxia may affect synaptic transmission (Mukandala, 2016; Gladman et al, 2010)
- Nutrients
- pH cellular
- pH CSF

Discussion

Emphasis has been placed on the role at the single neuron cellular level. While they may become involved in a pathophysiological process, their effect at this level and particularly in a persistent or chronic state is yet to be researched in relation to disturbed vertebral mechanics. If demonstrated, they may be a factor in vertebrogenic neurological factors which may exhibit at the clinical level as signs and symptoms.

Much of the cited research relates to neuronal changes or responses in the central nervous system involving the brain or spinal cord. Those findings have been adopted here to apply to neurons within the neural sleeve being an intimate extension of the spinal cord.

The general recognition of cervicogenic, and vertebrogenic conditions have been cited here in the medical science literature (Table 3) These clinical reports tend to support plausible concepts concerning nerve root, IVF, and neural transmission and manual segmental disturbances. It is suggested that the pathomechanics and pathoneurophysiology may contribute to explaining a range of neurogenic signs, symptoms, and syndromes. This association tends to justify biomechanical correction or modification. (Gatterman, 2005; Seaman & Winterstein, 1998; Leach, 1994; Haldeman, 1992)

The following range of clinical signs and symptoms are claimed to be vertebrogenic. Apart from mechanical nerve interference, it is suggested that the loss of vertebral facet motion could include an influence upon CSF flow within the IVF with resultant neural pathophysiology as one of the factors within some forms of a VSC.

From a clinical perspective, terms such as the following suggest recognition of their disrupted spinal origin: (Rome/Waterhouse 2023)

Table 2: Cited vertebrogenic clinical conditions

- Cervicogenic dizziness, (Chu et al, 2019; Reiley et al, 2017; Cleveland Clinic, 2022)
- Cervicogenic dysphagia, (Chu & Lee, 2021; Grgić, 2013)
- Cervicogenic dysphonia, (Hűlse, 2013; Kurkurin, 2004)
- Cervicogenic exophthalmos, (Wu, 2020)
- Cervicogenic headache, (Leone et al, 1998; Bogduk, 2001; Haldeman & Dagenais, 2001; Drottning et al, 2007)
- Cervicogenic migraine, (Anarte-Lazo et al. 2021)
- Cervicogenic otoocular syndrome, (Franz et al, 1999)
- Cervicogenic oesophageal dysfunction, (Vaňásková et al, 2001)
- Cervicogenic tinnitus, (Bechter et al, 2016)
- Cervicogenic vertigo, (Brown et al, 1992; Cleveland Clinic, 2022)
- Cervicogenic vestibule-ocular and post-concussion disorders. (Ellis et al, 2015)
- Vertebrogenic cardialgia, (Shakhnazarov et al, 1977; Sokov et al, 2009)
- Vertebrogenic cervicoencephalic syndrome, (Fengler et al, 1986)
- Vertebrogenic chest pain, (Grgić, 2007)
- Vertebrogenic dizziness, (Carrasco-Uribarren et al, 2021)
- Vertebrogenic dyspepsia (Rome & Waterhouse, 2022)
- Vertebrogenic dysphagia, (Walther, 1991; Andsersen & Fagerlund, 2000)
- Vertebrogenic vestibular dysfunction. (Likhachev et al, 1994)

Nociception

Kwok et al demonstrated that early peripheral joint injury activates joint nociceptors, which triggers a central spinal microglial response. Elevation of ATP in the CSF, and spinal expression of VNUT suggest ATP signalling may modulate communication between sensory neurons and spinal microglia at 2 weeks of joint degeneration. It would be fair to hypothesise from this that degenerative processes involving an intervertebral foramen may trigger a similar neural response. (VNUT = vesicular nucleotide transporter) (Cramer et al, 2004; Kwok et al, 2021)

It is suggested that pain can be more than a symptom and that it can have wider effects on health. This indicates that unless the cause of a pain is addressed a condition may be camouflaged by the symptom. (Zhang et al, 2022a) The wider ramifications may affect ambulation, psychological stress, loss of wages, substance abuse, and well-being. (Song, 2006; Zhang H et al, 2022; Zhang Z et al, 2022; Shirvalkar et al, 2023)

Importance of maintaining motion in this setting

While the health benefits of exercise are readily acknowledged, it is suggested that the mobile, flexible, supple spine with each segment moving freely and independently is an important component of a healthy functioning spine. Mobility exercises such as yoga tend to maintain this state of flexibility. Further, that a flexible state implies physiological motion of the intervertebral discs, facets and the prevention of fixations of those facets. As such, the pathophysiological conditions discussed here involving the intervertebral foramen, CSF changes, and effects on neural transmission may be minimised. (Batti'e MC et al, 1987; Harvard Health, 2015; Yang et al, 2015; Buran Çirak et al, 2021; Wu et al, 2022)

Conclusion

One of the actual mechanisms by which nerve transmission may be affected by mechanical vertebral displacement at the neuronal level is the focus of this study. The equivocal term '*nerve interference*' is hardly sufficient to identify the changes that may occur, and we should we consider the matter to be far more complex. Manipulative correction of such derangements would tend to explain the positive outcomes in a range of symptoms and conditions.

Our hypothesis

> We hypothesise that in considering the evidence presented, the physiology of healthy radicular neural tissue is optimally supported by physiological articular motion at each intervertebral foramen and segmental level.

The hypothesis is seen as relatively superficial compared to the complexity of neuronal physiology and pathophysiology and are open to modification and challenge.

The evidence tends to support the contention that IVF compromise can result in neurological consequences that may manifest as signs and symptoms.

When the IVF is considered from both an anatomical and physiological perspective, we note that such a complex and crowded site can function physiologically. However, there have to be limitations within that space that once exceeded, could lead to degrees of neural pathophysiology. Ultimately, further research should further explain the consequences arising from such a compromise and its functional, physiological, and clinical role

At the clinical level the presence of related signs and symptoms lead one to conclude that this compromise is pathophysiological, and importantly, potentially manageable through appropriate correction addressing dysfunctional articular restoration.

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Notes

The authors recall and would like to acknowledge the inspiration for this paper, by Watkins RJ, *Neurophthipsis of the Neurodokon*. (Circa 1960).

We acknowledge that some of the citations in relation to changes in neural physiology are extrapolated from instances involving the brain and spinal cord and applied this to nerve roots being part of the CNS.

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