Manual cervical therapy and vestibular migraine: A case series [version 2; peer review: 1 approved with reservations]

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Abstract

Background: Vestibular migraine (VM) is a relatively new diagnostic entity with incomplete knowledge regarding pathophysiological mechanisms and therapeutic guidelines. By reporting the effect of manual cervical therapy (MCT) on people with VM, we suggest a possible role for upper cervical afferents in VM treatment and/or pathogenesis. The objective was to describe the change in clinical presentation and self-reported symptoms of VM corresponding to MCT and followed up to six months.

Methods: A nonrandomised *ABA design was utilised to consecutively and prospectively evaluate selected patients with diagnosed VM. Symptom characteristics (frequency and intensity) were recorded along with standardised patient-reported outcomes (PROs) to document the response to MCT.

Results: Three patients were recruited who met the diagnostic criteria for VM. All three patients demonstrated improvement in both migraine attack and interictal symptom frequency. These improvements mirrored changes in PROs and were sustained over a six-month follow-up period.

Conclusions: The improvement that coincided with the intervention including MCT was rapid, observable and sustained. This suggests that the upper cervical spine could be a therapeutic target in VM and may have implications for future research into the pathogenesis of VM.

Keywords

Migraine, dizziness, vertigo, upper cervical spine, manual pressure, musculoskeletal dysfunction, physiotherapy, neck treatment, complementary and integrative medicine.
Plain language summary
Migraine is a complex disorder with many different factors potentially contributing to a person developing the condition. Whilst many different parts of the brain and body have been implicated as potential causes, the neck is often overlooked. To provide the best possible solution to patients suffering all forms of migraine, including vestibular migraine, a broader discussion must include all potential factors that may contribute to the disease developing, and/or contribute to optimal management. This article provides support for the upper neck to be included in that conversation, and provides the basis for further research to determine the significance of the neck in causing and/or treating this disorder.

Introduction
Vestibular migraine (VM) is a disorder characterised by episodes of specific vestibular symptoms, at least half of which are accompanied by features consistent with migraine (Lempert et al., 2012), and is considered to be the most frequent cause of episodic vertigo (Dieterich et al., 2016).

The diagnostic criteria for VM were formalised jointly by the Committee for Classification of Vestibular Disorders of the Bárány Society and the International Headache Society in 2012 (Lempert et al., 2012); hence, as a relatively new diagnostic entity, information regarding epidemiology is limited, with the one-year prevalence of VM (including ‘probable’ VM) estimated to be between 1.98% (Neuhauser et al., 2006) and 2.7% (Formeister et al., 2018).

Vertigo is a cardinal symptom for diagnosis of VM (Lempert et al., 2012), and therefore the ability of the cervical spine to cause vertigo as a symptom is central to any discussion regarding the upper cervical spine and VM. Some authors state overtly that ‘vertigo is not a symptom arising from the cervical spine’ (Reiley et al., 2017, p.2), whilst others consider vertigo a rare manifestation of traumatic neck pain, such that it is considered a useful symptom to differentiate from non-cervical causes of sensorimotor disturbance (Treleaven, 2017). The lack of established clinical evidence for upper cervical afferent contribution to vertigo may explain why it is not considered amongst the hypotheses for disorders contributing to the pathophysiological mechanisms underpinning VM, which currently include abnormal thalamic function, calcitonin gene-related peptide release into the inner ear and/or brainstem and/or cerebellum, genetic factors, abnormal processing of shared vestibular and nociceptive pathways, and cortical spreading depression (Furman et al., 2013). This appears discordant with clinical evidence indicating 25% of people with whiplash associated disorder report spinning as a symptom despite a lack of positive otoneurological findings (Treleaven et al., 2003). Similarly, case reports of what the authors termed ‘cervical vertigo’ (Brandt & Huppert, 2016), describe remission of vertiginous symptoms with resolution of neck pain. Clinical evidence is contingent on the presence of neck pain, however experimental evidence suggest non-painful afferents may also play a role in producing vertigo. Blocking afferents by injecting anaesthetic unilaterally in the upper cervical spine induced vertigo (sense of titling and falling) ipsilaterally (de Jong et al., 1977), whilst mimicking activation of cervical muscle spindles with vibratory stimulation results in both the visual environment moving contralaterally to the vibration (Jamal et al., 2020), and the sense of self-motion being either doubled (activated ipsilateral to side of rotation) or annulled (activated contralateral to side of rotation) (Panichi et al., 2011). Both clinical and experimental evidence suggest it is possible for upper cervical afferents (painful or non-painful) to contribute to vertigo as a symptom.

The potential impact of upper cervical muscle dysfunction on the sensorimotor system is underscored by their exceedingly high muscle spindle density (Kulkarni et al., 2001) and their convergence and antagonism with vestibular afferents at all levels of the central nervous system (CNS), including the central cervical nucleus (Hongo et al., 1988), external cuneate nucleus (Anastasopoulos et al., 1991), vestibular nuclei (Fredrickson et al., 1966), superior colliculus (Maeda et al., 1979), thalamus (Liedgren et al., 1976), cerebellum (Berthoz & Llinàs, 1974) and parieto-insular vestibular cortex (Shinder & Newlands, 2014).

The widely accepted model describing neural integration of afferent inflow from the vestibular, visual and proprioceptive systems was first proposed by von Holst and Mittelstaedt (von Holst & Mittelstaedt, 1950), whereby an ‘efference copy’ of the intended movement is subtracted from the feedback from self-generated movement or ‘reafference’. A perfect match results in sensory inflow from the vestibular system being cancelled (Figure 1a). Brooks and Cullen (Brooks & Cullen, 2014) demonstrated that aberrant feedback from upper cervical muscles failed to cancel vestibular reaference, leading to a summation of vestibular signals (Figure 1b) and resulting in vestibular symptoms.

Additional upper cervical afferents project to CNS regions believed to be involved in the pathophysiology of migraine. These include the trigeminocervical complex (Piovesan et al., 2003), hypothalamus (Malick et al., 2000), locus coeruleus (Cedarbaum & Aghajanian, 1978) and vestibular nuclei.
perceived handicap (measured by dizziness handicap inventory) with pharmacological treatment (antiepileptic drugs, calcium channel blockers, tricyclic antidepressants, beta-blockers, serotonin and noradrenaline reuptake inhibitors), diet modification and physical therapy vestibular rehabilitation (VRT). There were no double-blinded, randomised placebo-controlled trials available for this analysis and given the low quality of evidence and similar outcomes, no preference was found for one therapy over another (Byun et al., 2021). Whilst no manual therapy trials have been reported for VM, a systematic review and meta-analysis in migraine indicates similar effect between different modalities (physical therapy, relaxation biofeedback, chiropractic spinal manipulative therapy – CSMT) and prophylactic medication (topiramate, propranolol, amitriptyline), however a lack of control groups lowered the clinical utility of the results (Chaibi et al., 2011). This was further emphasised with a single-blinded placebo-controlled trial into CSMT in migraine finding equivocal improvement in the treatment and placebo groups (Chaibi et al., 2017). Despite attempts to identify ‘gaps’ in knowledge (Mallampalli et al., 2022) and the body of research linking upper cervical afferents to the production of vestibular symptoms in clinical, experimental and anatomical studies, their potential contribution to the pathophysiology of VM is consistently omitted, and MCT is not currently considered a therapeutic option.

The aim of this case series is to demonstrate the effect of a novel MCT approach on the clinical presentation and self-reported symptoms of VM. The approach described in part by Watson and Drummond (Watson & Drummond, 2014), involves assessment of asymmetrical response to transverse pressure (TP) at C2 spinous process (SP), which is treated using sustained digital ‘postero-anterior’ (PA) pressure to the C3 SP (Watson, 1997). Application of the technique caused modulation of nociceptive pathways as measured by the nociceptive blink reflex (Watson & Drummond, 2014), but validation as a treatment technique in a clinical population is lacking. This study aims to provide preliminary evidence in support of a novel MCT approach as a plausible modality for the treatment of VM and a basis for further research examining the role of upper cervical afferents in VM pathophysiology.

**Methods**

A systematic review and meta-analysis for treatment of VM indicates improvement in vertigo frequency and patient-reported perceived handicap (measured by dizziness handicap inventory) with pharmacological treatment (antiepileptic drugs, calcium channel blockers, tricyclic antidepressants, beta-blockers, serotonin and noradrenaline reuptake inhibitors), diet modification and physical therapy vestibular rehabilitation (VRT). There were no double-blinded, randomised placebo-controlled trials available for this analysis and given the low quality of evidence and similar outcomes, no preference was found for one therapy over another (Byun et al., 2021). Whilst no manual therapy trials have been reported for VM, a systematic review and meta-analysis in migraine indicates similar effect between different modalities (physical therapy, relaxation biofeedback, chiropractic spinal manipulative therapy – CSMT) and prophylactic medication (topiramate, propranolol, amitriptyline), however a lack of control groups lowered the clinical utility of the results (Chaibi et al., 2011). This was further emphasised with a single-blinded placebo-controlled trial into CSMT in migraine finding equivocal improvement in the treatment and placebo groups (Chaibi et al., 2017). Despite attempts to identify ‘gaps’ in knowledge (Mallampalli et al., 2022) and the body of research linking upper cervical afferents to the production of vestibular symptoms in clinical, experimental and anatomical studies, their potential contribution to the pathophysiology of VM is consistently omitted, and MCT is not currently considered a therapeutic option.

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**Methods**

This study protocol was developed in line with the CARE guidelines for reporting on case reports (Gagnier et al., 2013) and the CENT guidelines for reporting on N-of-1 trials (Vohra et al., 2015) in an attempt to minimise bias. Ethics approval was granted by the University of South Australia Human Research Ethics Committee (protocol number: 202637).

**Trial design**

A case-series methodology (Vohra et al., 2015) was employed with a nonrandomised *ABA* design, mimicking that of an N-of-1 study. Period *A* (i.e., run-in) was ‘usual care’ and varied in length based on the clinic waiting list and participant availability to commence treatment. The duration of period *A* and the nature of ‘usual care’ were not standardised for ethical reasons, as this would have involved delaying treatment.
Period ‘B’ was MCT. As is standard in physiotherapy practice, the nature, frequency and timing of the interventions were not standardised and were based on participant availability and treatment response in concert with an individual’s unique VM presentation. Period ‘A’ was postintervention. Participants did not commence any new interventions or change medications that could influence their VM symptoms throughout the data collection period (*ABA*).

**Eligibility criteria**

Three participants (two females aged 26 and 48, a male aged 43) who were diagnosed with VM by a neurologist and met the Bárány Society criteria for VM (*Lempert et al.*, 2012) sought treatment from the participating physiotherapist (RO). Participants were excluded from the study if they had a history of previous neck surgery or traumatic brain injury, recently started or changed medication or other treatment with the potential to influence VM (i.e., antidepressant medication, anxiolytics, analgesics, vestibular suppressants, VRT), had recently started or changed MCT to the cervical spine, or were diagnosed with another chronic pain condition (i.e., fibromyalgia, complex regional pain syndrome). Any potential participants who were unable to read the information sheet or demonstrate understanding of the study information presented if read to them or had insufficient cognitive capacity to provide voluntary written informed consent or impaired capacity to communicate verbally (i.e., aphasia) were excluded.

**Study setting and recruitment**

The study took place at a private physiotherapy clinic in Australia. Participants were prospectively identified at the time of booking their initial consultation. Administration or clinical staff screened each patient against the Bárány Society criteria for VM (*Lempert et al.*, 2012) and the study criteria. All potential participants were treated as study recruits; however, to avoid perceived coercion, individuals were not formally invited to participate until the end of period B. To avoid reporting bias, after period B, all prospectively identified individuals were invited to participate regardless of treatment response.

**Outcomes and analysis**

The primary outcome measures were symptom severity and frequency, and the use of pharmaceutical intervention, recorded in a diary tracking the presence and intensity of symptoms in period A* and the last 4 weeks of each subsequent review in period A, and therapist notes in period B. A 50% or greater change in symptom frequency over a 28-day period was considered significant (*Tassorelli et al.*, 2018). The symptom diary was recorded in paper form, and represented each symptom experienced by the participant on a particular day, approximate duration and intensity of each symptom, and amount of medication used if required. Diaries were presented on review and verified by the clinician with the participant during which time symptoms were classified in accordance with diagnostic criteria for VM (*Lempert et al.*, 2012). Accordingly, a migraine day was defined as a day during which the participant experienced vestibular symptoms (typically vertigo) lasting at least 5 minutes and up to 72 hours, at least half (in frequency) of which were accompanied by at least 1 migraine feature (migrainous headache, photophobia and/or phonophobia or visual aura). Any vertiginous episodes were recorded separately under internal vertigo (false sense of self motion) or external vertigo (false sense that the visual surround is spinning or flowing). Headaches, fatigue, and nausea were reported independently (*Lempert et al.*, 2012). Assigning a day as a ‘migraine day’ did not exclude it being counted as a vertigo or headache day, and as such the categories are not mutually exclusive. As such, a vertigo day may, or may not, have also been included as a migraine day, depending on the presence of other diagnostic features. Patient-reported outcomes (PROs) were used as secondary outcome measures and included the Headache Impact Test-6 (HIT-6), Dizziness Handicap Inventory (DHI), and the Depression Anxiety Stress Scale (DASS-21).

The impact of headache on daily life was assessed using the HIT-6, which is a validated six-item questionnaire generating total scores from 36 to 78, with scores ≥ 60 indicating severe impact (for full scoring see (*Yang et al.*, 2011)). In people with migraine, the within-person clinically meaningful change in the HIT-6 score over 12 weeks is estimated to be between -2.5 (mean change approach) and -6 points (ROC curve approach) (*Smelt et al.*, 2014). We have used the more conservative six-point change to indicate improvement.

The DHI (*Jacobson & Newman*, 1990) is a validated 25-item scale developed to assess the handicap caused by dizziness, with total scores ranging from 0 to 100. Total scores are divided into three handicap categories from mild (0-30) to moderate (31-60) and severe (61-100) (*Whitney et al.*, 2004). There is a standard error for test-retest indicating a minimal important change of 18 points from pre- to postintervention and three points using the ROC curve approach (*Friscia et al.*, 2014).

The DASS-21 is a valid and reliable measure used to detect symptoms of depression, anxiety and stress (*Antony et al.*, 1998), with subscales having independent cut-off scores (reported in (*Lovibond & Lovibond*, 1995)) for symptom severity that can be averaged to produce a composite measure. Minimum detectable change has been reported for each subscale as 3.86 (depression), 3.85 (anxiety) and 4.9 (stress) (*Ronk et al.*, 2013).

Clinical records were audited at the conclusion of each participant’s intervention period. Primary and secondary outcome measure data were extracted and input into Excel© (Microsoft, USA) along with details of the intervention delivered. Changes in VM attack features (frequency, severity and medication use) and impact (HIT-6, DHI and DASS-21) are presented descriptively as a series of cases using measures of ‘clinically meaningful change’ (*Jacobson & Newman*, 1990; *Ronk et al.*, 2013; *Smelt et al.*, 2014).
Interventions
No manipulative (localised, high-velocity thrust, low amplitude) techniques were applied. During period B, participants received an MCT intervention from a physiotherapist registered in Australia. In accordance with a specific protocol described in the introduction, manual assessment of the cervical spine determined the presence of asymmetrical response of C2 SP to TP with hypomobility typically present unilaterally. To restore a symmetrical response to TP palpation of C2 SP the therapist applied sustained digital PA pressure to the C3 SP (Watson, 1997). The direction and depth of pressure and the number and duration of sustained ‘holds’ were unique to each individual and appropriate for the participants’ presentations (determined by manual assessment of the neck). During the initial assessment education was also provided regarding the nature of the disorder (VM) and the potential role for upper cervical afferents, including a description of the manual assessment to follow. Subsequent treatments included demonstration of cervical retraction as a sustained stretch (20 seconds) repeated 4 times, to be done as a home exercise program up to 4 times per day (i.e. maximum 4 x 20 seconds x 4 times per day).

Due to the nature of a case series, data analysis was not conducted. However, to provide a description of change in self-reported measures pre- and postintervention, we used Hedges g effect size analysis (Shadish et al., 2015) with the magnitude of change interpreted using Cohen’s d recommendations of trivial (<0.2), small (0.2-0.49), medium (0.5-0.79) and large (>0.8) (Cohen, 1988). All collated data and effect size calculations are provided in Supplementary file 1.

Results
Cases and eligibility
Initially, four individuals were enrolled. However, one individual was excluded from the study prior to assessment due to the presence of comorbid fibromyalgia. Three eligible individuals reported having had at least five attacks, and all reported headache and visual and vestibular symptoms as features of their migraine presentation (see Table 1, Table 2, Table 3). The possibility of comorbid cervicogenic dizziness was excluded in all three participants as none demonstrated, neck pain and/or painful restriction of cervical range of motion (ROM) (Reiley et al., 2017). All participants tolerated the intervention, and no contraindications or adverse events related to the intervention were reported.

Participant 01 (P1)
Participant profile. P1 was a 26-year-old female with a three-year history of vestibular symptoms after contracting a viral illness while recovering from surgery. Initially, diagnosed with vestibular neuritis, P1 experienced frequent headache, suboccipital tension (without neck pain), orthostatic and head motion-induced dizziness, spontaneous vertigo, ‘slow, unclear and fuzzy’ vision, and nausea. Subsequently, diagnosed with anxiety, treatment with a psychologist was unsuccessful. Venlafaxine was prescribed after a neurologist diagnosed VM, resulting in a decrease in symptoms (reported as 70-80%), but P1 was still prone to acute exacerbations with triggers.

Venlafaxine was weaned after two years with symptoms stable for six to eight weeks before returning with daily interictal symptoms. Migraine prophylaxis with topiramate (not tolerated well and ceased after two weeks) and propranolol (80 mg) was recommenced seven months prior to assessment (start of period ‘B’) without improvement. Venlafaxine was reintroduced four months before assessment, with slight improvement in dizziness intensity but otherwise no obvious improvement in other symptoms. P1 suffered comorbid anxiety and depression and reported improvement in these symptoms with propranolol and venlafaxine.

Migraine attacks began with paraesthesia in both feet, progressing proximally through the legs and body, subsequently resolving to be replaced by vertigo, headache (NRS 8/10) and nausea. Attacks lasted from one to three days, easing to milder chronic daily headache (NRS 5/10) with vestibular symptoms, including spontaneous and orthostatic dizziness and sound-induced vertigo, every second day (see Table 1).

Key findings of manual assessment: Full, pain free cervical ROM. VBI testing comprised 10 seconds sustained end of range rotation and was asymptomatic; returning to midline produced a ‘visual spotting/white blotches’ lasting a few seconds. Standing balance – tandem stance, eyes closed (TSEC) was unremarkable. Palpation of the spinous process of C2 demonstrated deviation to the left of the midline. Transverse pressure on the C2 spinous process was asymmetrical with significantly more resistance to manual pressure from left to right when compared with right to left.

Intervention. Manual cervical therapy as described in Methods was provided. P1 had seven treatments over five weeks starting in September 2020, with two three-month nontreatment periods concluding in April 2021. A reassessment was conducted at the end of each nontreatment period.

Outcomes. Raw data are presented in Table 1, indicating improvement across all primary and secondary outcome measures. After initial treatment returning to neutral from sustained right cervical rotation produced no symptoms. P1 reported improvement in attack frequency from six migraine days per month (28 days) to no migraine days in the six-month nontreatment (follow-up) period. Interictal symptoms also showed improvement, with no symptom-free days in the run-in period changing to 21 symptom-free days (every 28 days) during the follow-up period.

Secondary outcome measures all showed clinically meaningful improvements during the treatment phase and continued to improve after the first four weeks of the nontreatment phase. After reporting increased feelings of anxiety and depression with significant life events during the nontreatment period, all scores regressed slightly for a short time before showing
sustained improvement at the six-month follow-up. Dosage of propranolol and venlafaxine also increased at this time, however improvement in primary outcome measures had already occurred during Period B.

Participant 02 (P2)

**Participant profile.** P2 was a 48-year-old female with a 14-year history of recurrent vertigo and head motion-induced dizziness triggering migraine attacks following surgery on a pituitary cyst. A bout of persistent motion sickness at age 14 was closely followed by a fall from a horse, resulting in low back pain (no head or neck trauma was reported). Recurrent headache and nausea developed twelve months later, progressively worsening over a three-year period, which included the onset of menstrual-related migraine without aura (age 16 years). At this time, nausea was constant, and multiple diagnoses from reflux to anorexia were given after losing 30 kg in weight over a four-year period.

Migraine attacks increased intensity and frequency after the birth of her last child, and after surgery on a pituitary cyst 14 years ago, symptoms worsened to include a ‘hemiplegic’ aura (weakness and numbness affecting one upper limb, facial drooping and dysarthria) and vertigo. Soon thereafter, P2 spent a week of 15 hours per day studying, after which she experienced ‘atypical trigeminal neuralgia’. The new ‘normal’ was chronic daily headache with nausea and lethargy, with bouts of dizziness and disequilibrium preceding intense nausea and severe headache.

P2 was diagnosed with VM by a neuro-otologist in July 2019 and prescribed amitriptyline, which was not tolerated well. P2 preferred meditation and manual therapy (chiropractic) for the daily headaches and low back pain, which would provide a reduction of symptoms for one to two days at best.

Migraine attacks began with intensification of interictal symptoms (nausea, dizziness and lethargy) and infrequently a scintillating scotoma. The scotoma gave way to suboccipital tightness and intense pressure in the retro-orbital regions and paroxysmal sharp ‘ice pick’ pain around the right orbit. Acute attacks lasted between three and five days, easing to interictal symptoms of chronic daily headache (NRS 5/10), nausea (5/10), dizziness and/or vertigo (4/10) and lethargy (6/10).
Key findings of manual assessment: Full, pain free cervical ROM. VBI testing comprised 10 seconds sustained end of range rotation. Increased anxiety while in left rotation eased on return to neutral but was followed immediately by vertigo – a sense of the body being pulled to the right. No symptoms to the right or on return to neutral. Standing balance – tandem stance, eyes closed (TSEC) was unable to be maintained > 10 seconds. Palpation of the spinous process of C2 demonstrated deviation to the right of the midline. Transverse pressure on the C2 spinous process was asymmetrical with increased resistance to manual pressure from right to left when compared to left to right.

**Intervention.** Manual treatment as described in Methods was provided. P2 had seven treatments starting in September 2020. The first five appointments were in the first two weeks, with the remaining two appointments over a two- and four-week period. A symptom diary and outcome measures (PRO) were recorded after successive three-month nontreatment periods concluding in March 2021.

**Outcomes.** Raw data are presented in Table 2, indicating improvement across all primary and secondary outcome measures. After initial treatment, P2 reported an immediate improvement with standing balance (TSEC) stable for 25 seconds and no feeling of anxiety or vertigo with return from sustained left rotation. Migraine attack frequency improved from 16 migraine days per month (per 28 days) to one migraine day during the treatment period and no migraine days in the eight months to the end of data collection. This is despite being admitted to the hospital with colitis during the first three-month nontreatment period, which is reflected in some of the outcome measures worsening during this period. Interictal symptoms also showed improvement.

**Table 2. Participant 2 Symptom features pre- and postMCT.**

<table>
<thead>
<tr>
<th>TIMEPOINT (W = week)</th>
<th>W₀ A - Run-in period</th>
<th>W₄ B - Rx block</th>
<th>W₁₂ A - 1 month post-Rx</th>
<th>W₂₃ 3 months post-Rx</th>
<th>W₃₉ 6 months post-Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average intensity (NRS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>5/10</td>
<td>5/10</td>
<td>1-2/10</td>
<td>3-4/10</td>
<td>1-2/10</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4/10</td>
<td>3/10</td>
<td>0-1/10</td>
<td>3-4/10</td>
<td>0-1/10</td>
</tr>
<tr>
<td>Nausea</td>
<td>5/10</td>
<td>3-5/10</td>
<td>0-1/10</td>
<td>3-5/10</td>
<td>4-5/10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Attack/symptom frequency per 28 days</strong></th>
<th>25 day diary (equivalent/28 days)</th>
<th>First 28 days of Rx block</th>
<th>28 day diary post-Rx</th>
<th>28 day diary 2–3 months post-Rx</th>
<th>28 day diary 5–6 months post-Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication</strong></td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>1 x metoclopramide</td>
<td>Nil</td>
</tr>
<tr>
<td><strong>Migraine</strong></td>
<td>14 (16/28)</td>
<td>1*</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>15 (17/28)</td>
<td>10</td>
<td>3*</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>19 (21/28)</td>
<td>11</td>
<td>3*</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>18 (20/28)</td>
<td>10*</td>
<td>3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>7 (8/28)</td>
<td>10</td>
<td>3*</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td><strong>Symptom free days</strong></td>
<td>4 (4/28)</td>
<td>16*</td>
<td>25</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td><strong>HIT-6</strong></td>
<td>63</td>
<td>48*</td>
<td>25</td>
<td>52*</td>
<td>36</td>
</tr>
<tr>
<td><strong>DHI</strong></td>
<td>72</td>
<td>28*</td>
<td>14</td>
<td>28</td>
<td>26</td>
</tr>
</tbody>
</table>

Rx (Treatment) I NRS (Numerical Rating Scale for pain) I *clinically meaningful change I (ES) Extremely severe, (S) - severe, (Mo) moderate, (M) mild, (N) normal
with four symptom-free days in the run-in period, with three of these occurring immediately after two chiropractic appointments to an average of 17 symptom-free days in the last month of each treatment-free period.

Secondary outcome measures showed clinically meaningful improvements during the treatment phase and continued to improve after the first four weeks of the follow-up phase. An episode of colitis caused an increase in nausea frequency, with a minimal increase in dizziness episodes; however, the perceived disability from dizziness worsened slightly.

Participant profile. Participant 03 (P3) was a 43-year-old male with a twenty-month history of VM of insidious onset. Whilst standing from a crouched position gardening, P3 hit the back of his head on a tree branch causing a slightly strained feeling in the neck; this passed almost immediately without further neck, head or other symptoms. Approximately one week later following the commencement of a new job, disrupted sleep with a newborn and a bout of gastrointestinal symptoms, P3 suffered persistent dizziness, accompanied by mild bilateral tinnitus, visual lag and nausea. Over several weeks the nausea and tinnitus eased completely and gave way to a persistent headache and a slight blurring of vision and visual lag with scanning, all of which were rarely absent. Rolling in bed, looking down at his phone, pushing his daughter in a pram or swing would induce vertigo and migraine attacks. These were preceded by paraesthesia in the suboccipital and occipital regions, followed by intensification of the baseline bilateral pressure headache (NRS 3/10) to moderate or severe headache (NRS 8/10), accompanied by internal vertigo (sense of falling), phonophobia (inducing severe nausea and exacerbating vertigo), and photophobia. Attacks would last for the remainder of the day, only relieved by sleep, and were moderate to severe intensity, preventing him from taking his daughter out in the pram and completing household tasks. The participant admitted being anxious about triggering attacks and feeling depressed about the impact it was having on his ability to engage with his daughter and maintain fitness.

After being diagnosed by an ENT specialist with persistent postural perceptual dizziness, P3 was referred to a neurologist who diagnosed VM. Amitriptyline, pizotifen, topiramate and propranolol were unsuccessful, and circadin helped sleep quality but did not improve the other symptoms.

Key findings of manual assessment: Full, pain free cervical ROM. VBI testing comprised 10 seconds sustained end of range rotation. No symptoms in left rotation or on return to neutral. No symptoms in right rotation – visual lag on return to neutral. Standing balance – tandem stance, eyes closed (TSEC) was unremarkable. Palpation of the spinous process of C2 demonstrated deviation to the right of the midline. Transverse pressure on the C2 spinous process was asymmetrical with increased resistance to manual pressure from right to left when compared to left to right.

Intervention. Manual treatment as described in Methods was provided. P3 was a fly-in fly-out oil rig engineer, and as such treatments were grouped initially according to his availability. After his initial consultation in September 2020 the next four treatments occurred during October before a two-week, and then a four-week review concluded in December 2020, with the first seven appointments occurring in the first five weeks. Symptom diary and outcome measures (PROs) were collected four weeks after the end of the last treatment and then again after two successive three-month nontreatment periods.

Outcomes. Raw data are presented in Table 3, indicating improvement across all primary and secondary outcome measures. After initial treatment, visual lag was absent on retesting return to neutral from sustained right cervical rotation. P3 reported improvement in attack frequency from two migraine days per month to no migraine days after treatment began, including during a six-month follow-up phase. Interictal symptoms also showed improvement, with P3 reporting no symptom-free days in the run-in period and averaging 18 days per month symptom-free in the last month of each three-month follow-up phase, which included 10 dizziness days after P3 had fallen off a roof. This was reinforced by a reduction in medication use, with only one maxalt taken as a preventive ‘insurance’ before an important interview, rather than due to symptoms/migraine attack.

Secondary outcome measures showed no change during treatment. During the first four weeks of the follow-up phase, secondary outcome measures improved dramatically; however, they showed some regression with the mild increase in dizziness after a fall from a ladder, reflected in the outcome measures at three months.

Discussion
The results of this case series demonstrate medium to large effects (Hedges’ g) of MCT on the clinical features (frequency, intensity, medication use) and self-reported symptoms (HIT-6, DHI, DASS-21) of VM in three consecutive and prospectively selected participants (see Supplementary file 1). Furthermore, no adverse reactions to treatment were reported. Reductions in all symptoms (migraine attacks and interictal symptoms) as well as PROs maintained medium to large effects over successive three-month nontreatment periods. Improvements in both the frequency of VM episodes and the interictal symptoms suggest a common underlying cause that was influenced by treatment including MCT.

Any attempt to explain why the clinical presentation of the participants in this study improved demands a cautious approach, not only because of the limitations inherent in case study design but also because the pathophysiology of VM remains uncertain (Mallampalli et al., 2022). It is this uncertainty that instigated a panel of experts to call for collaboration to elucidate the pathophysiological mechanisms underlying VM (Mallampalli et al., 2022) and provide the conditions for which case study research is well suited. That is, to contribute to the broader scientific discussion around the potential pathophysiology of
### Table 3. Participant 3 Symptom features pre- and postMCT.

<table>
<thead>
<tr>
<th>TIMEPOINT (W = week)</th>
<th>Average intensity (NRS)</th>
<th>Attack/symptom frequency per 28 days</th>
<th>Medication</th>
<th>Symptom free days</th>
<th>HIT-6</th>
<th>DHI</th>
<th>DASS-21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Headache</strong></td>
<td>16 day diary (equivalent /28 days)</td>
<td>Ibuprofen</td>
<td>0</td>
<td>73</td>
<td>80</td>
<td>D-34[N]</td>
</tr>
<tr>
<td></td>
<td><strong>Dizziness</strong></td>
<td></td>
<td>9* Panadol</td>
<td>0</td>
<td>74</td>
<td>80</td>
<td>A-20[ES]</td>
</tr>
<tr>
<td></td>
<td><strong>Dizziness</strong></td>
<td></td>
<td>Panadol 10</td>
<td>0</td>
<td>56*</td>
<td>20*</td>
<td>S-22[ES]</td>
</tr>
<tr>
<td></td>
<td><strong>Dizziness</strong></td>
<td></td>
<td>Circadin 2mg</td>
<td>1</td>
<td>57</td>
<td>42</td>
<td>D-10[ES]</td>
</tr>
<tr>
<td></td>
<td><strong>Migraine</strong></td>
<td></td>
<td>Ibuprofen</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>D-10[Mi]</td>
</tr>
<tr>
<td></td>
<td><strong>Headache</strong></td>
<td></td>
<td>Panadol 10*</td>
<td>4*</td>
<td>25*</td>
<td>59</td>
<td>D-0[N]</td>
</tr>
<tr>
<td></td>
<td><strong>Dizziness</strong></td>
<td></td>
<td>Ibuprofen 3*</td>
<td>0*</td>
<td>18</td>
<td>57</td>
<td>D-0[N]</td>
</tr>
<tr>
<td></td>
<td><strong>Dizziness</strong></td>
<td></td>
<td>Panadol 0*</td>
<td>0</td>
<td>25</td>
<td>57</td>
<td>D-0[N]</td>
</tr>
</tbody>
</table>

*a clinical meaningful change | (ES) Extremely severe, (S) - severe, (Mo) moderate, (Mi) mild, (N) normal

<table>
<thead>
<tr>
<th><strong>Medication</strong></th>
<th><strong>Migraine</strong></th>
<th><strong>Headache</strong></th>
<th><strong>Dizziness</strong></th>
<th><strong>Internal Vertigo</strong></th>
<th><strong>External Vertigo</strong></th>
<th><strong>Symptom free days</strong></th>
<th><strong>HIT-6</strong></th>
<th><strong>DHI</strong></th>
<th><strong>DASS-21</strong></th>
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</thead>
<tbody>
<tr>
<td>Ibuprofen 500mg</td>
<td>0</td>
<td>3*</td>
<td>0*</td>
<td>0</td>
<td>3*</td>
<td>0</td>
<td>D-10[A]</td>
<td>20*</td>
<td>A-20[ES]</td>
</tr>
<tr>
<td>Panadol 1000mg</td>
<td>0*</td>
<td>1</td>
<td>1*</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>A-16[S]</td>
<td>S-22[N]</td>
<td>S-22[ES]</td>
</tr>
<tr>
<td>Circadin 2mg</td>
<td>10*</td>
<td>0*</td>
<td>0*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>S-18[Mi]</td>
<td>42</td>
<td>D-10[Mi]</td>
</tr>
<tr>
<td>Ibuprofen 9*</td>
<td>0</td>
<td>0</td>
<td>0*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>A-2[N]</td>
<td>42</td>
<td>D-0[N]</td>
</tr>
<tr>
<td>Panadol 10*</td>
<td>0</td>
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<td>1*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>A-4[Mo]</td>
<td>34</td>
<td>D-0[Mo]</td>
</tr>
<tr>
<td>Ibuprofen 3*</td>
<td>0*</td>
<td>3*</td>
<td>3*</td>
<td>0</td>
<td>3*</td>
<td>25*</td>
<td>A-2[N]</td>
<td>34</td>
<td>D-0[N]</td>
</tr>
<tr>
<td>Panadol - 10</td>
<td>0</td>
<td>0*</td>
<td>0*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>A-4[Mo]</td>
<td>34</td>
<td>D-0[Mo]</td>
</tr>
<tr>
<td>Ibuprofen 0*</td>
<td>0</td>
<td>0</td>
<td>0*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>A-1[N]</td>
<td>34</td>
<td>D-0[N]</td>
</tr>
<tr>
<td>Maxigesic x 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxalt x 1</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rx (Treatment) | NRS (Numerical Rating Scale for pain) | *clinically meaningful change | (ES) Extremely severe, (S) - severe, (Mo) moderate, (Mi) mild, (N) normal

A disease, particularly when the view may be seen as counterintuitive or contrarian (Vandenbroucke, 2001). Speculation regarding the possible reason for effects observed with our three participants serves to propose novel directions for future investigation.

The focus of our hypothesis centres around a key finding in all our participants: palpable asymmetries of the upper cervical spine and resistance to transverse pressure on the spinous process of C2. In combination, these findings were clinically interpreted to represent hypertonicity of the ipsilateral obliquus capitis inferior (OCI) (a hypothesis requiring validation). Of the many CNS regions that are potentially affected by this purported muscle dysfunction, it is interesting to note that the locus coeruleus (LC) has been shown to be sensitive to small asymmetries in trigeminal muscle afferent input (De Cicco et al., 2014), the correction of which has a demonstrable impact on cognitive function (De Cicco et al., 2016). Beyond cognition, the LC has been linked to numerous aspects of migraine pathophysiology, including cortical spreading depression (purported to underpin migraine aura (Goadsby et al., 2017)) and pain modulation (Vila-Pueyo et al., 2019), plays a role in anxiety and depression (Poe et al., 2020), and has been linked to the comorbidity of anxiety with vestibular disorders (Balaban et al., 2011). In this light, it is interesting to note that the asymmetries and resistance noted at C2 were resolved during treatment with sustained pressures on the spinous process of C3. All participants demonstrated complete resolution of symptoms associated with sustained end of range cervical rotation immediately after resolution of asymmetry to resistance to transverse pressure at C2. Non-VBI symptoms have been reported in subjects with persistent post-traumatic headache during more prolonged (60 second) sustained neck rotation testing (Hammerle et al., 2023a), which were subsequently correlated with sub-occipital muscle pressure sub pain thresholds (Hammerle et al., 2023b),...
providing some support to our hypothesis regarding OCI. In addition, resolution of asymmetry to TP at C2 coincided with changes in our participants’ primary and/or secondary outcome measures, providing a direction for further research.

While it is clear that the participants in this case series improved (see Table 1–Table 3 and Supplementary file 1), it is impossible to attribute improvement to a specific aspect of treatment. The ‘real world’ nature of these treatments encompass a multimodal approach, where MCT is provided in conjunction with education and a single stretching exercise. It is therefore possible that any one of these modalities, some of them in concert, or indeed none of them (placebo or natural history) rather than MCT alone, is responsible for the changes observed. Indeed, participant 1 was using migraine prophylaxis (venlafaxine and propranolol) and had these dosages increased in the follow-up period A, after a significant reduction in symptoms had already occurred during period B.

As a case series, we are limited by the lack of a control group and sample size power and are open to the potential confounding factors associated with selection bias (Nissen & Wynn, 2014). We have attempted to minimise bias by recruiting participants consecutively and prospectively, conducting this study in accordance with the CARE guidelines for reporting case studies and the CENT guidelines for reporting on N-of-1 trials (Gagnier et al., 2013; Vohra et al., 2015). Previously, the natural history of VM was reported in an observational study of 61 patients followed up over nine years. Recurrent vertigo was observed in 87% of patients with 44% unchanged or worse and with 56% with some reduction in frequency (Radtke et al., 2012). While not impossible, spontaneous remission in three participants with long histories of symptoms seems highly implausible. Expectation of a positive outcome is crucial to a placebo response (Benedetti, 2013). While it is well accepted that manual therapy (MT) provides a placebo effect (Bialosky et al., 2017), these effects have been assessed in conditions that would traditionally be treated with MT. As none of our participants experienced neck pain or restricted ROM supporting a ‘cervicogenic dizziness’ diagnosis and MCT is not considered a treatment for VM (Byun et al., 2021; Mallampalli et al., 2022), it seems unlikely that these individuals had a ‘strong’ if any expectation of a positive result. The exception is participant P2, who had undergone chiropractic MT for many years for lower back problems. This included treatment of the neck, which provided relief for one to two days, possibly giving some belief that the neck was implicated.

Conclusion
This case series demonstrates an observable, rapid and sustained impact on the clinical presentation and medium to large effects in self-reported symptoms of VM in three prospectively and consecutively recruited patients. VM is a relatively new diagnostic category with currently unclear pathophysiology and treatment pathways. It is therefore important that all hypotheses regarding pathophysiology be considered and tested and that novel treatment options be considered. Despite the known pathoanatomical and pathophysiological pathways linking the upper cervical spine to regions explaining symptom behaviour, the upper cervical spine is not readily considered in current pathophysiological explanations for VM. The challenge of proposing a hypothesis involving the upper cervical spine for conditions involving migraine and vertigo is not lost on the authors. In light of this, we echo the sentiments of May (May, 2020), urging readers to remain open to all possible mechanisms associated with migraine and vertigo to inform a broader approach to managing these patients.

In conclusion, this case series suggests that this MCT approach may represent a safe, well-tolerated and affordable option with the potential for rapid and sustained relief of symptoms in some patients with VM and advocates a legitimate avenue of scientific enquiry for treatment and pathophysiological mechanisms of VM.

**Data availability**
**Underlying data**
No data are associated with this article.

**Extended data**

This project contains the following underlying data:

- Supplementary file 1 Manual Cervical Therapy and Vestibular Migraine (Clinical outcome measures – tabulated symptom diary data and patient reported outcome measure data for 3 participants from baseline to 6 months post treatment, recorded in excel spreadsheet to calculate Cohen’s D and Hedges’ g)
- Participant Statement – P01 (Statement from study participant 01 regarding impact of disease, management prior to and during the study period)
- Participant Statement – P02 (Statement from study participant 02 regarding impact of disease, management prior to and during the study period)

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

**Acknowledgements**
The authors would like to thank Prof Alan Pearce for assistance with data analysis and feedback on the preparation of this manuscript.
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Cedarbaum JM, Aghajanian GK: Early vestibular processing does not discriminate from passive self-motion if there is a discrepancy between predicted and actual proprioceptive feedback. J Neurophysiol. 2014; 111(12): 2465-2478. 

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Major comments
This is generally an interesting paper. There are major revisions required to improve the validity of this paper (see below).

SPECIFIC COMMENTS

INTRODUCTION -

Overall, the introduction contains a lot of information that is likely irrelevant to the topic and certainly doesn't match the possible hypothesis of the discussion. I suggest that it is rewritten to reflect this.

Second paragraph - co-morbidity doesn't equal causality. Might be better to rephrase to suggest that only many migraine patients suffer from dizziness that might also be a spectrum of VM and thus the incidence could be higher.

Third paragraph need to first establish the diagnostic criteria of VM and then show the similarity to whiplash. Cervical vertigo is not a suitable term, only 25% of the whiplash patients reported vertigo.

Fourth paragraph - greater MSK is not supported by a recent SR- Liang et al 2019. (Liang, Galea et al. 2019)¹. This sentence is not needed to make the point from previous paragraph supporting cervical afferents for contributing to the cause of dizziness. Suggest remove the first sentence. Could also suggest a possible trigger for migraine, rather than a direct cause of the symptoms e.g. (Malhotra, Pace et al. 2020)². Could also refer to recent articles suggesting a possible autonomic
trigger from the upper cervical region. (Hammerle, Lu et al. 2022, Hammerle, Thomas et al. 2022)\(^3\), \(^4\).

Paragraph 7 – need to discuss current treatment evidence for VM (Byun, Levy et al. 2021)\(^5\) as well as current evidence for manual therapy for usual migraine as well. There have been some trials e.g. (Chaibi, Tuchin et al. 2011, Herranz-Gómez, García-Pascual et al. 2021, Varangot-Reille, Suso-Martí et al. 2022)\(^6\),\(^7\),\(^8\). Thus the aim of the study is to demonstrate effect of this specific MCT in VM. Need to also discuss this particular technique and approach and how it is different.

**METHODS**

Ethical clearance required?

This sentence does not make sense – please clarify. “Subsequently, absence of neck pain and/or limitation of cervical ROM in all three participants eliminated concurrent ‘cervicogenic dizziness’ as an alternate or comorbid diagnosis (Reiley et al., 2017).”

Need reference for 50% reduction in frequency.

Is the hit 6 most suitable for VM- headache?

Need more information re: the diary. How collated etc.

Intervention- should state all that was done here included stretches etc.

The manual technique is a form of MT and should also be introduced in the introduction.

Not clear what the difference between migraine, headaches, internal and external vertigo. These measures need to be described in the methods.

**RESULTS**

P1- was there a history of normal migraine prior?

Table 1 – need to be clear about what all these are e.g. is headache number of headaches in the 28 days? Also ensure all relating to clinically meaningful change is depicted in the tables as well. Interventions state it was PA pressure at C3 but in patient 1 it was transverse pressure to C2- or is that just assessment findings?

Also dose of propranolol significantly increased during that time as well. Why was this done? This should be mentioned in the results.

P2. Why was sustained neck rotation done? Was this also done in P1? Reference this test?

P3 had a hit to the back of the head would that be exclusion? (Participants were excluded from the study if they had a history of previous neck surgery or traumatic head injury”. Perhaps state why this was an exclusion criteria in the first place or refine the statement?
Tables should be uniform. Perhaps put primary outcome measures first and then secondary outcome measures.

Present summary of effect sizes as well in results.

**DISCUSSION -**

Discussion is better description of possible relationships between the neck and VM in these patients than the introduction. This further highlights that a lot of the introduction is not necessary as it doesn't relate to the discussion. Could also refer to sustained cervical rotation and these articles (Hammerle, Lu et al. 2022, Hammerle, Thomas et al. 2022) to help your point in the introduction and revisit in the discussion3,4.

Need to state why Patient 1 increased dose of medication.

“it seems unlikely that these individuals had a ‘strong’ if any expectation of a positive result.”- but how were the patients referred to the clinic? They sought and paid for treatment so there was likely some belief that it would work.

Perhaps stress in the conclusion it might only be some patients, some bias in selection of VM patients.

**References**


**Is the background of the cases' history and progression described in sufficient detail?**
Partly

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**
Partly

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**
Partly

**Is the conclusion balanced and justified on the basis of the findings?**
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** neck pain, dizziness, headache, concussion. I am not an expert at n of 1 trials.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.