Alternating headache: C2-3 guilty or not?

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Unilateral headache and the behaviour of unilaterality underpins diagnostic criteria in the medical classification of headache. However, the medical model of headache admits to a lack of understanding of the mechanism of unilateral alternating headache.

A (medical) attempt was made in the late 1980s which hypothesised involvement of (intracranial) structures in or closely adjacent to the midline, with the pathologic state being duplicated contralaterally as it spreads across the midline.

Alternating side-locked headache mimics alternating lateral lumbar list / shift which is thought to be a result of alternating aberrant lumbar intra-discal behaviour; could C2-3 intra-discal disc behaviour be responsible for alternating headache? My clinical experience suggests that it is responsible. Undoubtedly though, lumbar and cervical discs are structured differently, which suggests extrapolation from lumbar to cervical discs is tenuous.

However, this review of contemporary research, which dispels widely held beliefs of intervertebral cervical (and ageing of) discs, not only supports, but strengthens my hypothesis.

LEARNING OUTCOMES
TO SUPPORT PHYSIO FIRST QAP

1. Be abreast of contemporary research regarding cervical discs.
2. Be aware of the challenges to conventional teaching and paradigms.
3. Understand why an alternating headache is a musculoskeletal event.

Introduction

Side-locked headache literally means a unilateral headache which is always on the same side.

A pain syndrome presenting always on one side immediately suggests an anatomically circumscribed pathophysiological mechanism. Similarly, a fixed location, unilateral side-locked headache suggests involvement of a precise structure, however, the "structure" for unilateral headache has not been determined (Leone *et al* 2008; Da Silva *et al* 2012).

Unilateral pain has long been considered a hallmark of cervicogenic headache (CeH). However, according to orthodox medical perspectives, a unilateral headache which alternates or shifts sides either between episodes or within an episode precludes a diagnosis of CeH (Sjaastad & Fredriksen 2000, 1998; Fredriksen *et al* 2015). This caveat has been introduced by medical professionals not experienced in musculoskeletal medicine (Becker 2010) and needs to be challenged for, as with unilateral side-locked headache, the reason/s for side-shift of unilateral headache are unclear (Leone *et al* 2008).

My clinical experience of 24,000 hours with more than 8,000 headache and migraine sufferers suggests otherwise. A unilateral headache which alternates either between episodes, or within an episode, is a CeH; alternating headache is a "musculoskeletal event". Alternating unilaterality has been erroneously considered to be a trait of primary headache, denying many headache and migraine persons appropriate treatment because disorders of the upper cervical spine are denied a causative role in primary headache (Goadsby & Bartsch 2008).

Epidemiology

The main unilateral side-locked primary headache conditions are migraine, cluster headache (CH), paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and hemicrania continua (HC).

While the literature reports varying proportions of side-locked and alternating unilateral primary headaches, it does reflect data from two clinic-based studies on strictly unilateral headaches (Ramon *et al* 2013; Prakash & Rathore 2016). Pooled data of the diagnostic distribution of side-locked primary headache from both studies (n=407) is outlined in table 1.

Primary headaches constitute 61% of all side-locked headaches. In the clinic setting CH was the most common side-locked headache (20%). Almost one-third of patients had either secondary headaches or neuralgias, with CeH the

> "IN PATIENTS WITH SIDE-LOCKED HEADACHE, C2 IS ALMOST INVARIABLY ROTATED AWAY FROM THE SIDE OF THE HEADACHE"

HEADACHE	% OF PATIENTS
Primary headache	61.7
Migraine	14
Cluster headache	19.9
Paroxysmal hemicrania SUNCT	3.2
SUNCT	4.2
Hemicrania continua	7.3
Secondary headache	34
Cervicogenic headache	8.1
Other secondary headaches and neuralgias	

TABLE 1: Pooled data of diagnostic prevalence of patients with unilateral, side-locked headache in clinic setting (n=407) (Ramon *et al* 2013; Prakash & Rathore 2016)
Note: Primary headache is one where the pathophysiology is unknown; Secondary headache where the headache is secondary to a known pathophysiology or cause.

most common side-locked secondary headache (8.1%).

Pooled data from Ramon *et al* (2013) and Prakash & Rathore (2016) demonstrating the prevalence of side-locked and alternating unilateral primary headaches is summarised in table 2.

Aside from the focus on alternating unilateral headache, and side-locked unilaterality being a key diagnostic criterion of CeH (Sjaastad & Fredriksen 2000; Sjaastad *et al* 1998; Fredriksen *et al* 2015), and therefore indicating that CeH theoretically should be included in differential diagnosis (Prakash & Rathore 2016), table 2 also demonstrates that a significant proportion of migraineurs and cluster headache sufferers are candidates for a skilled examination of their upper cervical spine.

The hypothesis

I am often asked to explain the underlying cervicogenic mechanism responsible for alternating headache. The explanation begins with "alternating headache is the C2-3 equivalent of an alternating lumbar list", and immediately the sceptic announces that extrapolation from lumbar discs is tenuous because cervical discs are structured differently and therefore behave differently? Before I address these concerns, here are some clinical observations, laced with research.

Rotation of the axis (C2) is relatively easy to identify, even for the novice manual therapist. An interesting observation in patients with side-locked headache is that C2 is almost invariably rotated away from the side of headache, therefore the spinous process (SP) of the C2 is deviated to the side of headache, ictally, i.e. when the headache is present, and interictally, i.e. when there is an absence of headache.

PRIMARY HEADACHES	% OF SIDE-LOCKED UNILATERALITY	% OF ALTERNATING HEADACHE
Migraine	17	83
Cluster headache	69-72	31-28
Paroxysmal hemicrania	85-97	15-3
SUNCT	80-88	20-18
Hemicrania continua	92-100	8-0

TABLE 2: Percentage of patients with unilateral side-locked and alternating unilateral headache in primary headache disorders (Ramon *et al* 2013; Prakash & Rathore 2016)
Note: Even though tension-type headache is considered a bilateral headache and generally not considered in the differential diagnosis of side-locked headaches, there may be a subset (4-36%) of patients with side-locked headache (Sjaastad & Fredriksen 2000; Prakash & Rathore 2016)

In patients with alternating headache the SP of C2 is deviated to the side of headache irrespective of the side of headache (ictally), that is, if the patient presents with left-sided headache, the C2 SP will be deviated to the left; when examining the same patient during right sided headache, the SP is deviated to the right.

Examining a patient (interictally) with alternating headache, and whose headaches occur more frequently on one side, it may be noted that the SP of C2 is deviated to the side of increased frequency. For example, if 7/10 headaches occur on the right, then the SP will be deviated to the right. This presentation mimics the lateral shift or trunk-list associated with development of acute low back pain which is a common clinical event (Gillan *et al* 1998). In this case the patient's torso is translated or shifted contralaterally or away from the pain, e.g. during an episode of left lumbar pain, the patient's torso is shifted to the right, during an episode of right-sided lumbar pain the torso shifts to the left. Furthermore, as is the case in the lumbar spine, inexact treatment directed specifically at C2-3 can lead to the headache (or low back pain) changing sides within seconds, with concomitant rotation of C2 in the opposite direction.

Currently, the exact mechanism of lateral shift in the lumbar spine remains speculative, however the shift is widely accepted as being associated with disc pathology (Porter & Miller 1986; McKenzie 2003; Suk *et al* 2001). A seminal study of 45 patients (Suk *et al* 2001) demonstrated that lateral shift was associated with, and away from the side of lumbar disc herniation. This is the strongest evidence yet to support the hypothesis that an alternating lumbar list is underpinned by intradiscal disturbances.

While recognising that extrapolation of lumbar disc behaviour to cervical discs is controversial (Mercer & Jull 1996; Mercer & Bogduk 1999), it is tenable that hypomobility of the CO-C2 intervertebral segments places increased strain on the C2-3 intervertebral disc (Pfaffenrath *et al* 1988). The consequences of subsequent ongoing micro trauma to the C2-3 intervertebral segment are significant, as this is viewed as the foundation of upper cervical motion (Pfaffenrath *et al* 1988); a transitional segment perhaps analogous to L5/S1 or C7/T1. Normal C2-3 movement is essential for optimal upper cervical function (Watson 2017; Sizer *et al* 2005).

Notwithstanding that headache can result from intradiscal disturbances (Schellhas *et al* 1996; Grubb & Kelly 2000), rotation of C2 is pivotal. Inferior obliquus capitis (IO) attaches to the SP of C2 and its diagonal arrangement puts it in the prime position to rotate C2. In doing so, IO spasm not only stresses C1-2, C2-3 and, because of its attachment to C1, CO-C1; this mechanism stresses all three potentially headache referring segments simultaneously. Moreover, recent research demonstrated manual cervical reproduction of accustomed head pain (a key diagnostic criterion of cervicogenic involvement in headache) in 95% of migraineurs, all of whom experienced alternating, unilateral head pain (Watson & Drummond 2012).

While recognising that IO does not traverse the C2-3 segment, perhaps because of its proximity and very high proprioceptive content (Kulkarni *et al* 2001), it is acutely sensitive (to react) to un-physiological, alternating, asymmetrical C2-3 intradiscal pressure (table 3).

So, my hypothesis has arrived back to the beginning and the fundamental question of whether the C2-3 is capable of behaving like a lumbar disc; vulnerable to at least asymmetrical, un-physiological distribution of intradiscal pressure.

The C2-3 disc

Alternating unilateral headache impersonates an alternating lumbar list, therefore I have used the lumbar disc model to explain the alternating behaviour of unilateral head pain. However, the findings of seminal

> "RECENT RESEARCH HAS DEMONSTRATED MANUAL CERVICAL REPRODUCTION OF ACCUSTOMED HEAD PAIN IN 95% OF MIGRAINEURS"

MUSCLE	DENSITY OF SPINDLES PER GRAM OF MUSCLE TISSUE
Inferior obliquus capitis	242
Superior obliquus capitis	190
Rectus capitis posterior major	98
Rectus capitis posterior minor	98
Longus Colli	48.6
Multifidus	24.3
First Lumbrical	16.5
Trapezius	2.2
Latissimus Dorsi	1.4

TABLE 3: Density of muscle spindles per gram of muscle tissue (Kulkarni *et al* 2001)

research largely demonstrate that cervical discs are structurally different from lumbar discs (Mercer & Jull 1996; Bogduk 2012).

Unlike the annulus fibrosus (AF) of lumbar discs, those of cervical discs do not comprise concentric layers of collagen, and the AF of cervical discs are much more substantial anteriorly, being supported by the anterior longitudinal ligament than posteriorly through the posterior longitudinal ligament (Mercer & Jull 1996; Bogduk 2012). Mercer & Jull (1996) conclude that "a separate and new model must be devised for the cervical discs" and a statement that appears to be beyond question, that "… such pain cannot be ascribed to postero-lateral fissures in the anulus fibrosus as it is in the lumbar spine…", although it should be noted that my hypothesis is not necessarily about pain.

However, does the fact that they are structurally different mean that cervical and lumbar discs behave differently from one another? In context with this hypothesis, and notwithstanding that the posterior annulus is relatively (to the lumbar spine) deficient, i.e. it is only 1.0 mm thick, and some interpret "deficiency" as an absence (de Bruin *et al* 2016), it does exist and is innervated. Sinuvertebral nerve fibres enter through the postero-lateral portion of the AF and form a dense, fine nerve fibre network in the deep layer of the intervertebral portion of the (alar) posterior longitudinal ligament and the superficial layer of the AF (Bland & Boushey 1990).

Mercer & Jull (1996) also state that "posteriorly the nucleus is contained only by alar fibres of the posterior longitudinal ligament, under which or through nuclear material must pass if it is to herniate." Indeed, a nuclear bulge and herniation are demonstrated on page 622 of their paper (Mercer & Jull 1996). While the posterior annulus might not contribute significantly to restraining a bulge, because of its existence it will be subject to tension in the event of a nuclear bulge or even an asymptomatic, asymmetrical distribution of intradiscal pressure. Indeed, the diaphanous nature of the posterior annulus would likely render it ultrasensitive to relatively subtle, and most likely radiologically indiscernible, intradiscal pressure differentials. Moreover, muscle spindles react to provide appropriate motor responses to abnormal afferent information. The ipsilateral inferior obliquus capitis, because of its proximity and abundance of spindles, is the prime candidate to respond, rotating C2 contralaterally.

However, all of this is contingent upon the existence and viscosity of the nucleus pulposus (NP) as there is the view that the viscous, gel-like NP transforms to a more rigid fibrocartilaginous mass (Mercer & Jull 1996; Bland & Boushey

1990). What is the future of the ageing NP? Is it devoid of viscosity?

The nucleus pulposus

Advanced technologies have made it possible to perform more sophisticated in-vitro and in-vivo studies and biochemical analyses. A recent in-vitro study (Fontes *et al* 2015) investigated the extracellular matrix and collagen profile of cervical discs in those of under 35 years, and over 65 years of age. Thirty cervical discs per group were obtained during autopsies of presumably-asymptomatic individuals. The investigators analysed the discs using MRI, a morphological grading scale, light microscopy, scanning electron microscopy (SEM) and immunohistochemistry for collagen types. The findings most pertinent to my hypothesis is that SEM demonstrated the NP as a separate structure which persists in older discs; this distinction boundary was not evident with MRI or light microscopy (Fontes *et al* 2015).

Quantitative MRI protocols have been used to evaluate T2 (relaxation times) in the intervertebral disc (Blumenkrantz *et al* 2010; Hoppe *et al* 2012; Marinelli *et al* 2010; Nagashima *et al* 2012; Stelzeneder *et al* 2012; Takashima *et al* 2012; Wang *et al* 2013, 2014; Watanabe *et al* 2007; Welsch *et al* 2011; Driscoll *et al* 2016). T2 is a time constant, characterising signal decay and is the time required for a viscous substance to recover from a shearing stress after flow has ceased. T2 is a measure of water content which has been shown to correlate strongly with disc biochemical composition, such that decreased T2 values indicate decreased disc water content (Marinelli *et al* 2009; Tertti *et al* 1991). The most recent of these studies (Driscoll *et al* 2016) assessed 10 asymptomatic subjects; five males and five females with a mean age of 41.8 ± 12.3 years. The lateral view of each disc, from C2-C3 through to C7-T1, was imaged using a 3.0 TMR scanner, and a sagittal multi-slice, multi-echo sequence of the intervertebral discs was divided into five regions of interest, centred along the mid-line of the disc extending anteriorly and posteriorly. The NP and AF demonstrated increased T2 moving distally from C2-3, and T2 was greater than outer regions in the NP in the C6-7 and C7-T1 implying a viscosity differentiation between the AF and NP (Driscoll *et al* 2016). The latter finding suggests that superior discs have a more homogenous water composition, i.e. less distinction between the NP and AF, except for the C2-3 disc where the T2 values were high in relation to intervening discs, and similar to C6-7 and C7-T1, i.e. the C2-3 disc demonstrated a similar distinction between the NP and AF (Driscoll *et al* 2016). The authors hypothesised that "… these differences may be due to the unique anatomy of the C2 vertebrae, which likely induces alterations in composition and lifespan changes compared to other discs" (Driscoll *et al* 2016). This finding reinforces a biomechanical "transitional" role of the C2-3 segment (Watson 2017) and the importance of optimum function of this segment, as it is considered the substratum of upper cervical movement (Sizer *et al* 2005).

In summary, the increase (relative to C3-4, C4-5 and C5-6) in T2 values C2-C3, C6-C7, and C7-T1; the spatial homogeneity in T2 values (water content) was observed for the mid-cervical discs, i.e. decreased distinction between the NP and AF, whereas the NP and AF distinctions persisted at C2-C3, C6-C7, and C7-T1, i.e. increased T2 in the NP compared to AF; were seen individually in almost all subjects throughout the age range.

Other researchers have investigated glycosaminoglycans (GAGs) in cervical discs. The AF and NP vary substantially in the content of the two main macromolecular components; collagen and aggrecan (Tertti *et al* 1991), the latter being a large proteoglycan attached with approximately 100 GAG "side chains" (Haneder *et al* 2013), about 50% of which are in the NP, and 10–20% in the AF (Urban & Winlove 2007), whereas the distribution of collagen is the opposite with around 20–30% in the NP and 70% in the AF (Saar *et al* 2012). GAGs are important to maintain IVD tissue fluid content (Urban & Winlove 2007; Eyre & Muir 1977), while aggrecan provides intervertebral disc and cartilage with the ability to resist compressive loads. The localised high concentrations of aggrecan provide the osmotic properties necessary for normal tissue function with the GAGs producing the swelling (predominantly of the NP) pressure that counters compressive loads on the tissue. This functional ability is dependent on a high GAG / aggrecan concentration being present in the tissue extracellular matrix (Urban & Winlove 2007; Roughley *et al* 2006).

> "SCANNING ELECTRON MICROSCOPY DEMONSTRATED THE NUCLEUS PULPOSUS AS A SEPARATE STRUCTURE WHICH PERSISTS IN OLDER DISC"

In a recent in-vivo study (Bostelmann *et al* 2017), 96 AF and NP fractions of 12 surgically removed discs, from nine patients with a mean age of 45.9 years (SD± 10.1) and a male:female ratio of 4:5, were biochemically analysed for GAG content.

Analyses revealed significantly higher GAG content in the NP when compared to the AF, and GAG concentrations were higher in the posterior than the anterior portion of the AF. The authors speculated that the higher GAG content posteriorly correlated with zones of higher strain (Bostelmann *et al* 2017), perhaps indicating that the posterior aspect of the AF is subject to more tension.

The recent literature demonstrates that the NP is a clearly defined (distinct from the AF) entity in the C2-3 intervertebral disc. Furthermore, the presence of GAGs and increased T2 values confirms viscosity exists. Additionally, these characteristics are evident in the fourth and fifth decades of age. Collectively, this body of research is in contradistinction to previous findings that the NP is "a deep core of undissectable fibrocartilaginous material" (Mercer & Jull 1996). and an earlier study (Oda *et al* 1988) where the infantile NP was found to be replaced by "fibrocartilage and dense fibrous tissue in the first half of the second decade" and, in the adult disc leads "… up to obliteration of the disc."

These discoveries also appear to be at odds with findings (Mercer & Jull 1996) that show the abundant evidence of symptomatic and asymptomatic cervical disc bulges across ages ranges (Schellhas *et al* 1996; Boden *et al* 1990; Matsumoto *et al* 1998; Lehto *et al* 1994; Siivola *et al* 2002; Teresi *et al* 1987; Okada *et al* 2011; Nakashima *et al* 2015). In the most recent of these studies, Nakashima *et al* (2015) reviewed MRIs of 1,211 asymptomatic subjects; 87.6% presented with cervical discs bulges which, in terms of frequency, severity, and number of levels, increased significantly with increasing age.

Summary

To rule out CeH, i.e. "… the reasons are unclear" (Leone *et al* 2008), because of alternating unilateral head pain is groundless and is no more than a "neurological" opinion. My own hypothesis is based on unparalleled clinical experience and neuro anatomical principles, and describes a mechanism for unilateral, alternating headache.

Recent research suggests that the NP, as distinct from the AF, of the C2-3 disc is a vibrant entity. Furthermore, it is not unreasonable to postulate that subtle, postero-lateral, or initially central which progresses to become unilateral, intradiscal pressure differentials impact on the posterior disc elements. The alternating headache mechanism comprises a "chain reaction" initiated by:

- alternating posterolateral aberrant C2-3 intradiscal pressure, which…
- increases pressure, not necessarily symptomatic, on the ipsilateral (alar portion of) posterior longitudinal ligament and adjacent delicate AF…
- activating the ipsilateral IO, rotating C2 contralaterally, i.e. SP of deviates ipsilaterally to the asymmetrical aberrant intradiscal pressure, thereby stressing CO-C1, C1-2 and C2-3 simultaneously.

Alternating or side-shift behaviour is a significant feature of CeH, and alone is sufficient for a diagnosis of CeH. Furthermore, I would contend that unilateral head pain that radiates, as the headache develops, to include the other side is underpinned by a similar mechanism. Side-locked unilaterality is an expression of consistent ipsilateral (to headache) aberrant C2-3 intradiscal pressure.

The question of the origin of alternating unilateral headache is problematic and ignored by the medical model of headache; the silence is deafening. Irrespective of my hypothesis being validated, the manual cervical clinical management of alternating, and side-locked unilateral headache does not change; alternating unilateral headache is a musculoskeletal event.

I rest my case…

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About the author

Dean is the Founder of the Watson Headache® Approach, which is now recognised internationally for its unparalleled diagnostic accuracy and uncomplicated innovative clinical reasoning. He has presented and taught internationally since 1995 and, because of his unique experience with more than 8,000 headache and migraine clients, continues to be sought after as Clinical Consultant at the Watson Headache® Clinic and Educationalist at the Watson Headache® Institute.

Dean has recently completed his PhD at Murdoch University in Perth, Western Australia, in which he investigated the role of upper cervical spine; his vision is that a skilled examination of the upper neck is genuinely accepted as a legitimate, routine practice when investigating headache and migraine conditions.

In the little spare time he has, Dean designs logos and book covers, enjoying a glass of pinot while preparing the evening meal, or "extending" his cardiovascular system at the gym!

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