



The
**Ehlers
Danlos**
Society™



EDS ECHO SUMMIT SERIES

P R E S E N T A T I O N

A Physician's Perspective on Cranio-cervical Instability

S P E A K E R

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Content of Presentation

- Headache and neck pain - common symptoms in clinic
- Complex symptoms at the craniocervical junction
- Relationship between symptoms, signs and imaging
- General principles of management of cervical pain and instability
- Summary

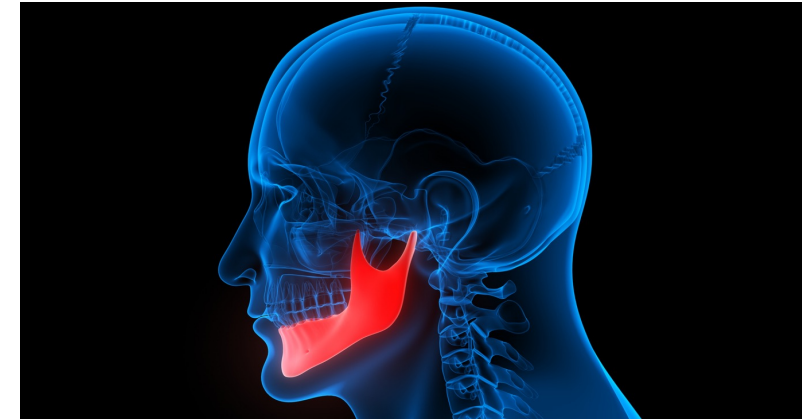
Musculoskeletal concerns at the Neck in Hypermobility-related Disorders



Joint, Soft tissue, and Neurological concerns related to the head and neck

Ligament laxity

Strength, posture, Proprioception impairment



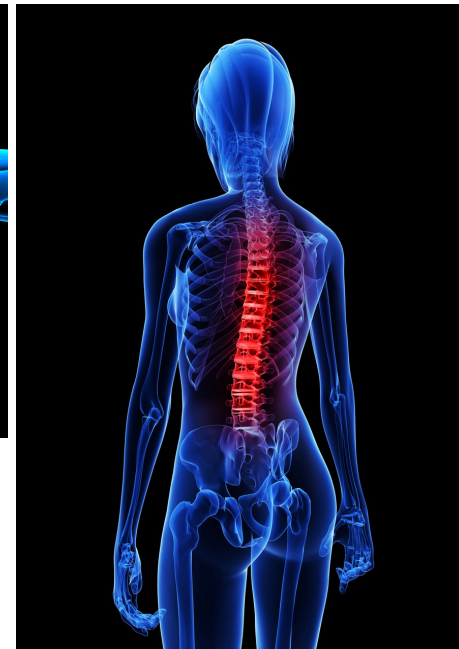
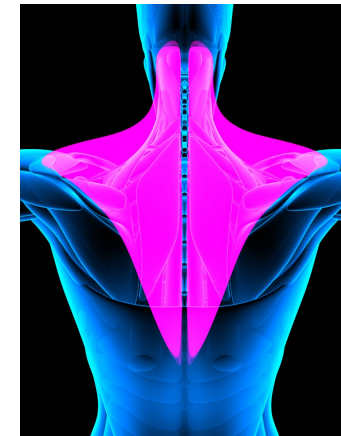
Increased range of movement

-Extension

-Flexion

-Rotation

Unstable movement



TMJs, shoulder girdle and thoraco-lumbar spine.



In clinic cohort studies headache and neck pain are common presentations in patients with hypermobility-related disorders



Malhotra A, Pace A, Ruiz Maya T, et al. Headaches in hypermobility syndromes: A pain in the neck?. *Am J Med Genet A*. 2020;182(12):2902-2908.

Barnett J, Rowe V, Hunter J et al. 2017. <https://www.neurokc.com/wp-content/uploads/2017/07/AHS-Role-of-Hypermobility-in-Headache12.pdf>

Henderson FC Sr, Austin C, Benzel E, et al. Neurological and spinal manifestations of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017;175(1):195-211.

Castori M, Morlino S, Ghibellini G, et al. Connective tissue, Ehlers-Danlos syndrome(s), and head and cervical pain. *Am J Med Genet C Semin Med Genet*. 2015;169C(1):84-96.

Neilson D, Martin VT. Joint hypermobility and headache: understanding the glue that binds the two together--part 1. *Headache*. 2014;54(8):1393-1402.

Hakim AJ, Grahame R, Non-musculoskeletal symptoms in joint hypermobility syndrome. Indirect evidence for autonomic dysfunction?, *Rheumatology*, 2004: 43(9),1194–1195

Bendik EM, Tinkle BT, Al-shuik E, et al. Joint hypermobility syndrome: A common clinical disorder associated with migraine in women. *Cephalalgia*. 2011;31(5):603-613.

Hakim AJ, Grahame R, Non-musculoskeletal symptoms in joint hypermobility syndrome. Indirect evidence for autonomic dysfunction?, *Rheumatology*, 2004: 43(9),1194–1195



Some individuals with hypermobility-related disorders present with craniocervical junction (CCJ) instability.

Malhotra A, Pace A, Ruiz Maya T, et al. Headaches in hypermobility syndromes: A pain in the neck?. *Am J Med Genet A*. 2020;182(12):2902-2908

Henderson FC Sr, Rosenbaum R, Narayanan M, et al. Atlanto-axial rotary instability (Fielding type 1): characteristic clinical and radiological findings, and treatment outcomes following alignment, fusion, and stabilization. *Neurosurg Rev*. 2021;44(3):1553-1568.

Henderson FC Sr, Austin C, Benzel E, et al. Neurological and spinal manifestations of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017;175(1):195-211.

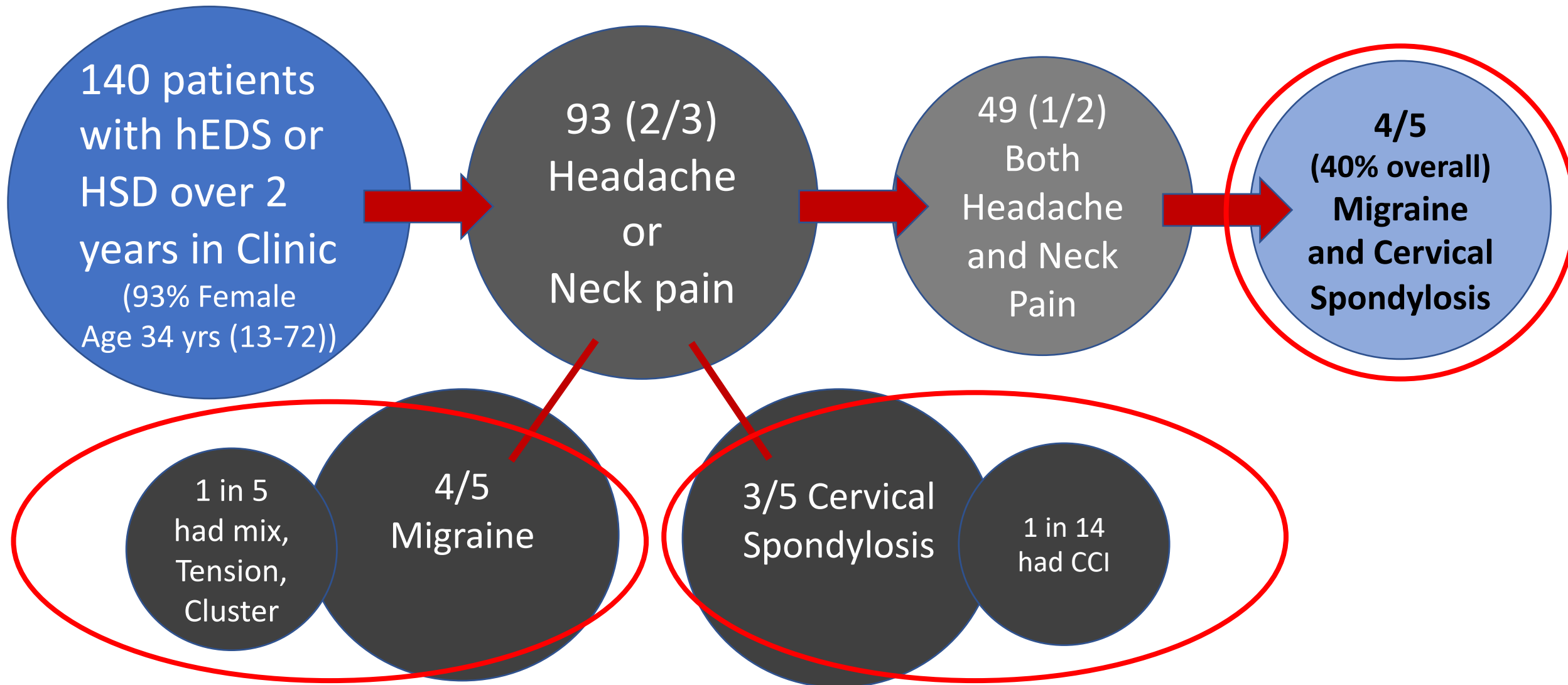
Henderson FC (2016) Cranio-cervical Instability in Patients with Hypermobility Connective Disorders. *J Spine* 2016 (5) 299

Milhorat, T.H., Nishikawa, M., Kula, R.W. *et al*. Mechanisms of cerebellar tonsil herniation in patients with Chiari malformations as guide to clinical management. *Acta Neurochir* 152, 1117–1127 (2010).

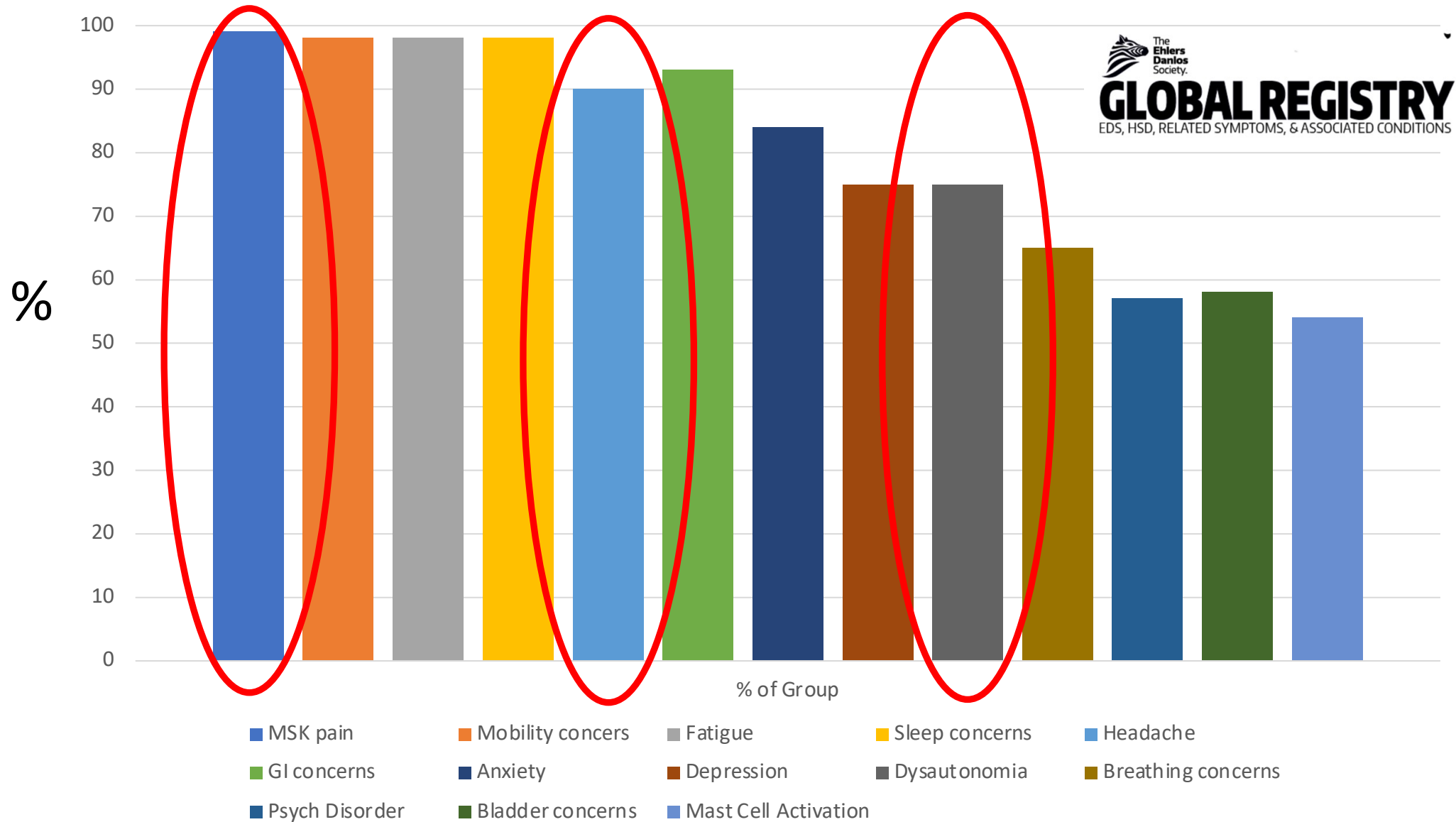
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Proportion of Group Reporting Symptoms and Comorbidities (n=1334) Global Registry, The Ehlers-Danlos Syndrome



Chronic Migraine



Chronic Migraine prevalence in the general population:

0.5-1.5%

Greatest in females

Peak age, 40s

Represents 7-8% of all migraine

Buse DC, Manack AN, Fanning KM, et al. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. *Headache*. 2012;52(10):1456-1470

Chronic migraine is over-represented in EDS and HSD people attending general clinics.

Hakim AJ, Grahame R, Non-musculoskeletal symptoms in joint hypermobility syndrome. Indirect evidence for autonomic dysfunction?, *Rheumatology*, Volume 43, Issue 9, September 2004, Pages 1194–1195

Bendik EM, Tinkle BT, Al-shuik E, et al. Joint hypermobility syndrome: A common clinical disorder associated with migraine in women. *Cephalalgia*. 2011;31(5):603-613.

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Cervical Spondylosis



Presents in the majority of general population by the age of 50 (asymptomatic and symptomatic)
Peak age of identifiable disease on imaging – 40s

Symptoms most commonly reported (Wang et al. (n=1276) were:

- Pain 87%
- Dizziness 55%
- Weakness and tingling in the neck and arms 51%
- Headache 28%
- Vertigo and unsteady gait 15%
- Nausea and vomiting 14%
- Neck stiffness 12%

Wang C, Tian F, Zhou Y, He W, Cai Z. The incidence of cervical spondylosis decreases with aging in the elderly, and increases with aging in the young and adult population: a hospital-based clinical analysis. *Clin Interv Aging*. 2016;11:47-53. Published 2016 Jan 12. doi:10.2147/CIA.S93118

Cervical Spondylosis



Most common findings on MRI in the general population (age 52 (19-87), n=611) with chronic neck pain were (Jensen et al.):

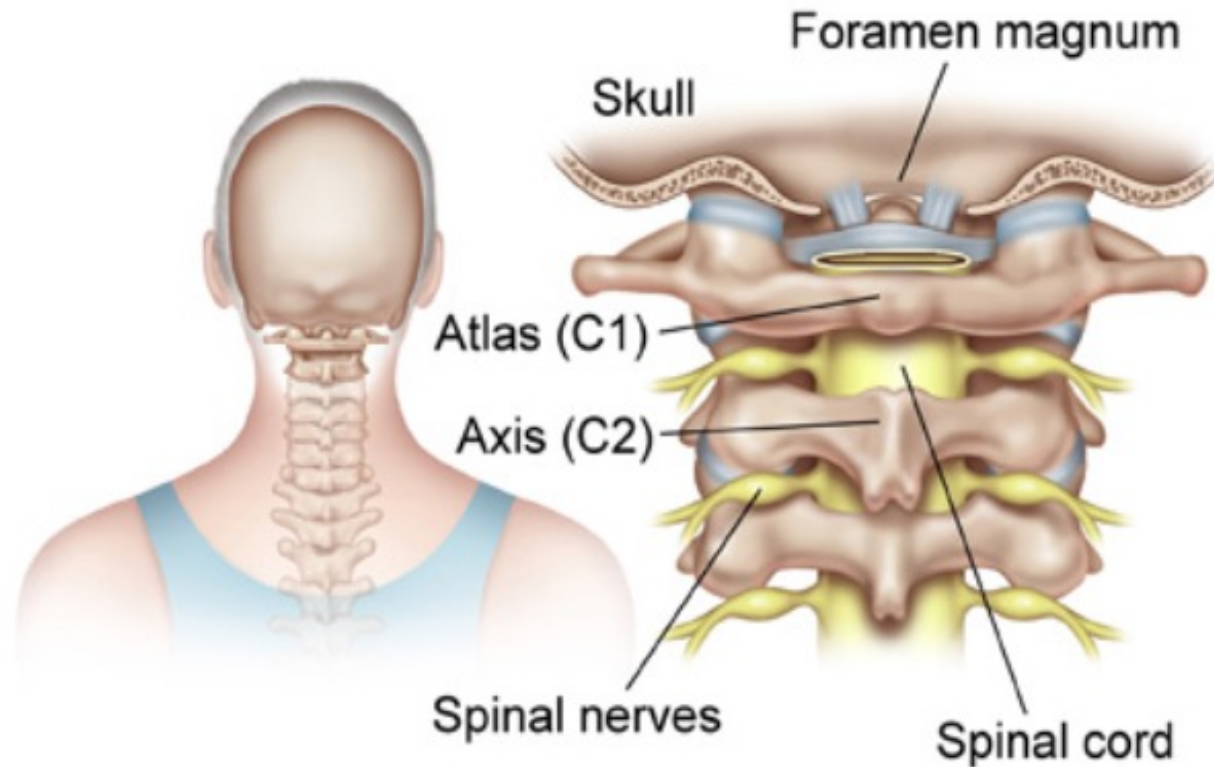
Foraminal stenosis 50-75%

Uncovertebral joints arthrosis (C3 to C7) 75%

Disc degeneration 67%

Nerve root compression 2%

Jensen RK, Jensen TS, Grøn S, et al. Prevalence of MRI findings in the cervical spine in patients with persistent neck pain based on quantification of narrative MRI reports. *Chiropr Man Therap*. 2019;27:13. Published 2019 Mar 6. doi:10.1186/s12998-019-0233-



Cervicogenic: C1-3 nerve entrapment

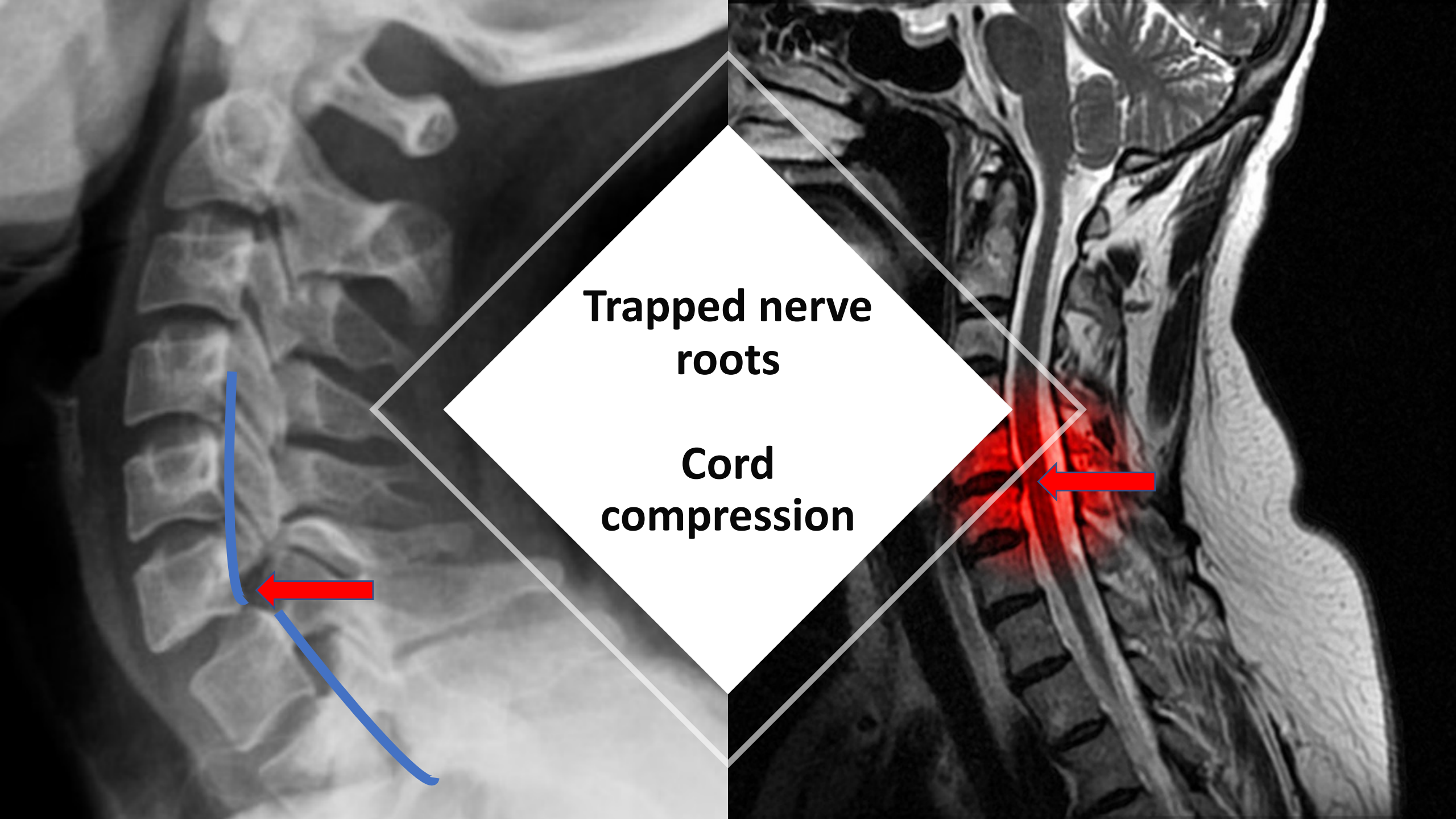
1-4% of people with headache

Cervical Radiculopathy:
1-5 per 1000 general
population

No specific data on prevalence in EDS and HSD

Al Khalili Y, Ly N, Murphy PB. Cervicogenic Headache. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; March 8, 2021

Mansfield, M, Smith, T, Spahr, N, Thacker, M. Cervical spine radiculopathy epidemiology: A systematic review. *Musculoskeletal Care*. 2020; 18: 555– 567



Trapped nerve roots

Cord compression

Cervical Spondylosis



Cervical spondylosis is as common in EDS and HSD as the general population but potentially arising in a younger age group Averaging 33 +/- 2-6 years

Malhotra A, Pace A, Ruiz Maya T, et al. Headaches in hypermobility syndromes: A pain in the neck?. *Am J Med Genet A*. 2020;182(12):2902-2908.

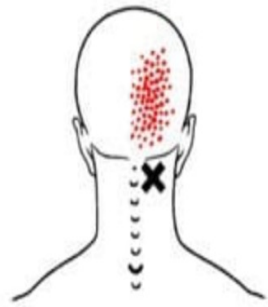
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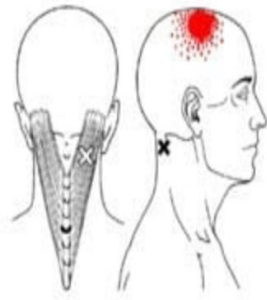
Masseter



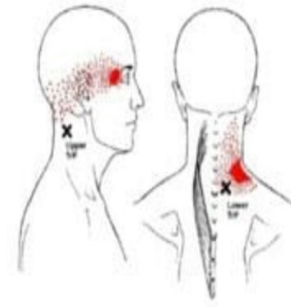
Semispinalis Capitis



Semispinalis Capitis



Splenius Capitis



Splenius Cervicis



Sernocleidomastoid



Sternocleidomastoid



Suboccipital Muscles



Temporalis



Upper Trapezius

Tension Headache

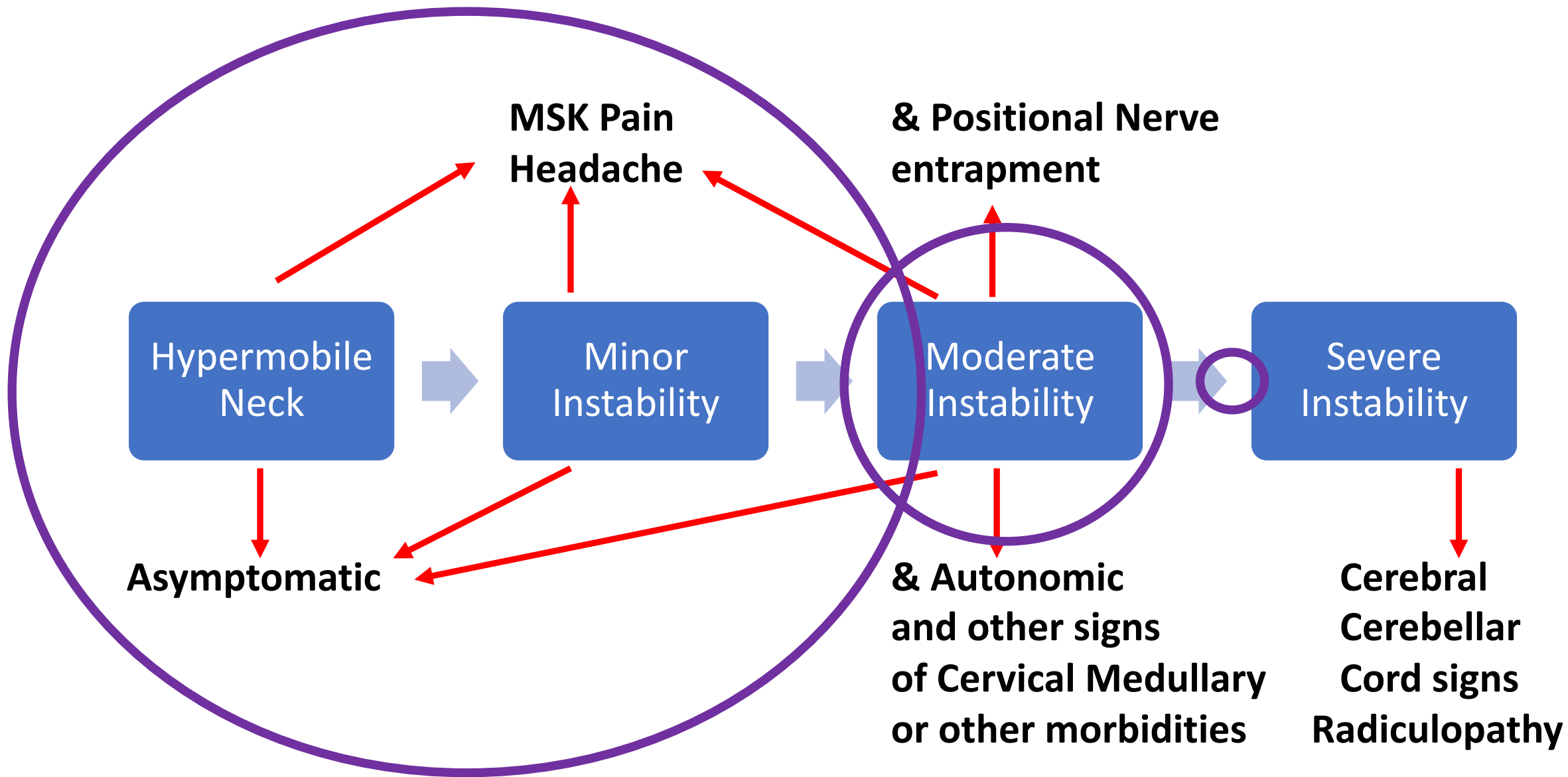
Overall, 10-20% general population

Frequent, 10%

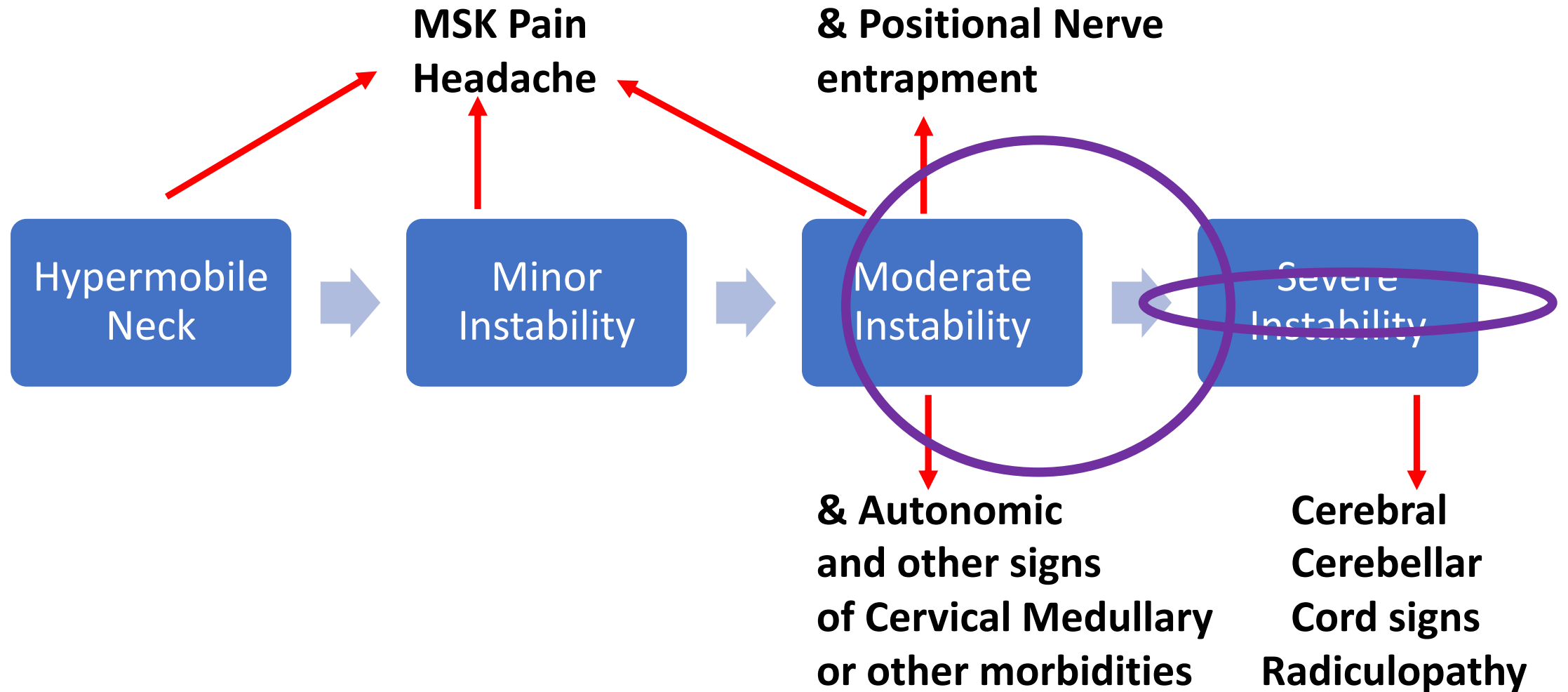
Chronic, 1%

Ferrante T, Manzoni GC, Russo M, et al. Prevalence of tension-type headache in adult general population: the PACE study and review of the literature. *Neurol Sci.* 2013;34 Suppl 1:S137-S138.

Data on Tension Headache suggests it is not over-represented in EDS / HSD



Developed from:
 Steilen D, Hauser R, Woldin B, Sawyer S. Chronic neck pain: making the connection between capsular ligament laxity and cervical instability. *Open Orthop J.* 2014;8:326-345.



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The Craniocervical junction:

Surface of the skull

Atlas (C1)

Axis (C2)

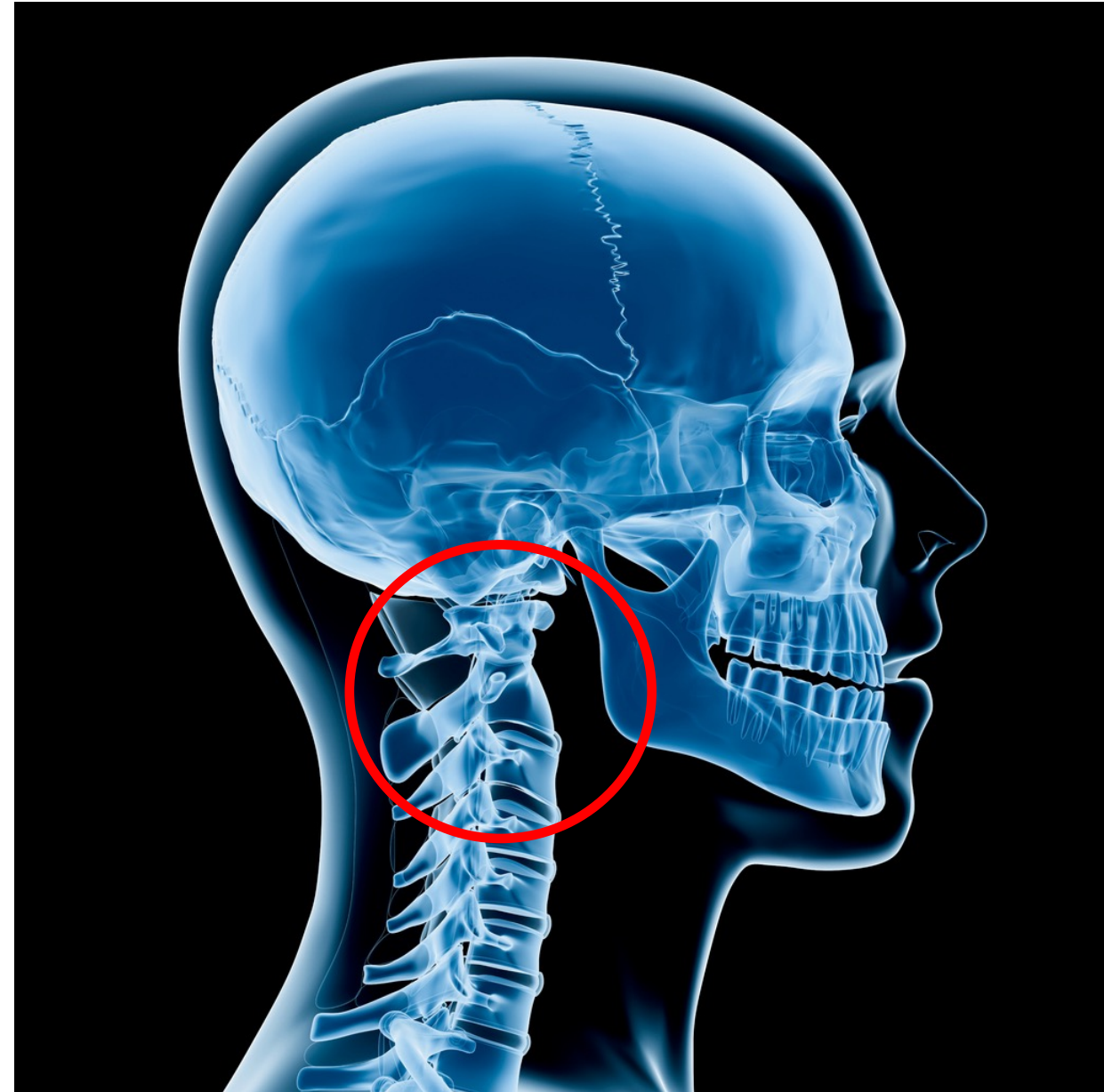
Muscles and connective tissues
attaching the skull to the cervical
spine.

Spans:

Brain stem and upper cord

Encephalic vasculature

Cerebrospinal fluid (CSF) cisterns.



The Craniocervical Junction

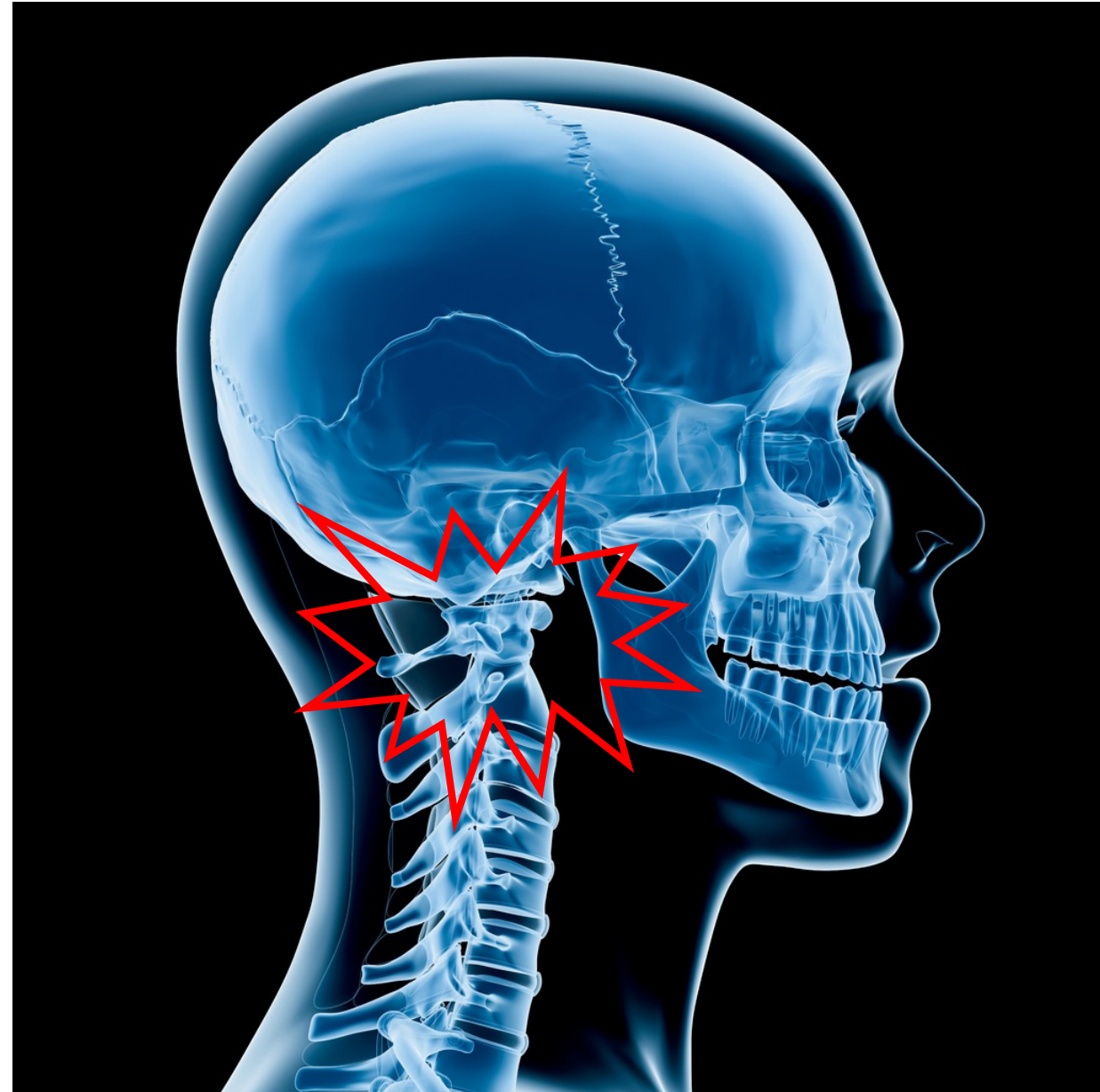
Malformation and malalignment at the CCJ can cause pressure or tension changes leading to signs and symptoms:

C1/2 nerve roots

Cerebellar, brainstem and upper cord

Changes in CSF flow & intracranial pressure

Changes in vascular flow





- Headache
- Neck pain

- Cerebral
- Autonomic
- Cord and Nerve root sensorimotor concerns

nature of symptoms depends on site of compression or tension

- Cervical Medullary syndrome

While the vast majority of patients with HM-R disorders with neck pain and headache do not have signs of overt cord compression or nerve root compression...

some with EDS or HSD present with a real sense of instability ('Wobble head' 'head too heavy'), neck cracking / clicking, and unease / foreboding related to movement, and combination of features that constitute the Cervical medullary syndrome

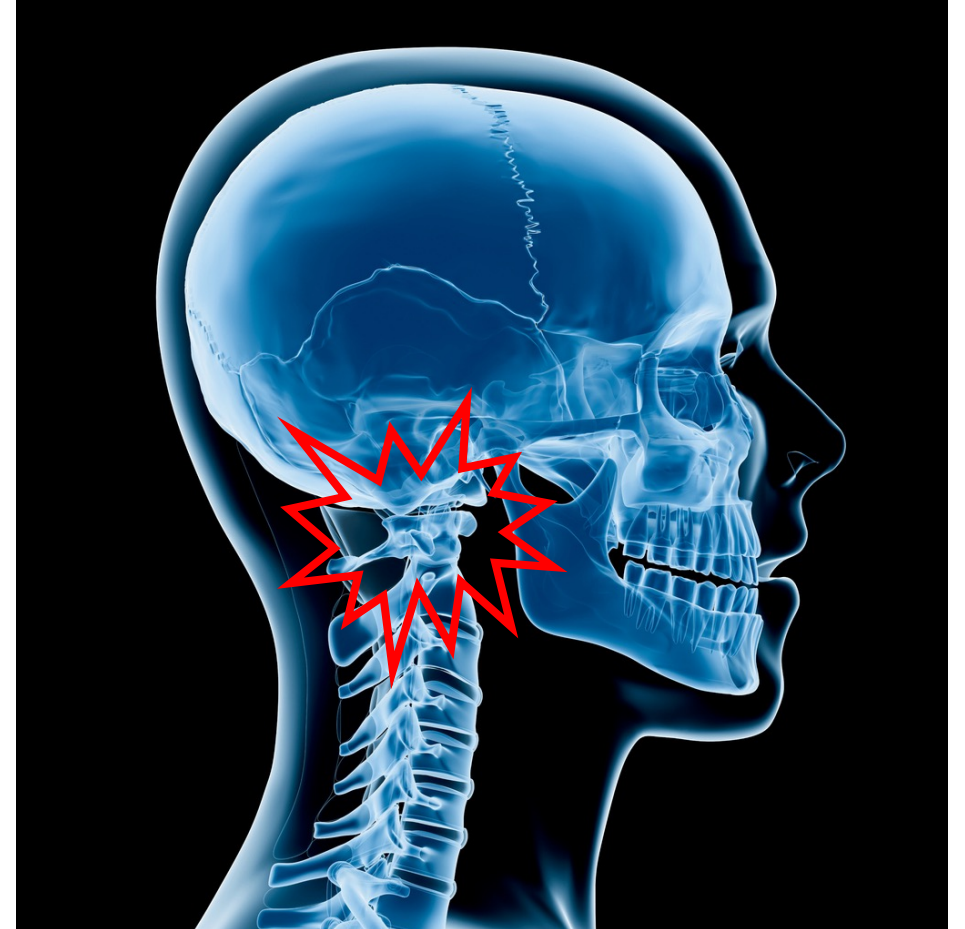
Henderson FC et al. 2016, 2017, 2021

Symptoms and Signs of CCJ Instability

Cervical medullary syndrome

A constellation of concerns:

- Headache
- Neck pain
- Double vision
- Vertigo
- Tinnitus
- Memory loss
- Difficulties swallowing
- Difficulty breathing
- Autonomic dysfunction
- Numbness in the arms and legs
- Arms and legs feel weak
- Clumsy, unsteady gait...



Challenge for the Clinician and The Patient

Cervical medullary syndrome

A constellation of concerns:

- Headache
- Neck pain
- Double vision
- Vertigo
- Tinnitus
- Memory loss
- Difficulties swallowing
- Difficulty breathing
- Autonomic dysfunction
- Numbness in the arms and legs
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- Clumsy, unsteady gait...

Or Something else?

- There are several reasons for headache e.g., TMJD, migraine,
- Neck pain is common
- As are visual disturbances
- Tinnitus is very common in the general population
- Laryngeal issues may explain swallow and breathing concerns
- Swallowing may be affected by oesophageal dysmotility
- Autonomic symptoms / proprioceptive changes / musculoskeletal concerns...all common in EDS and HSD

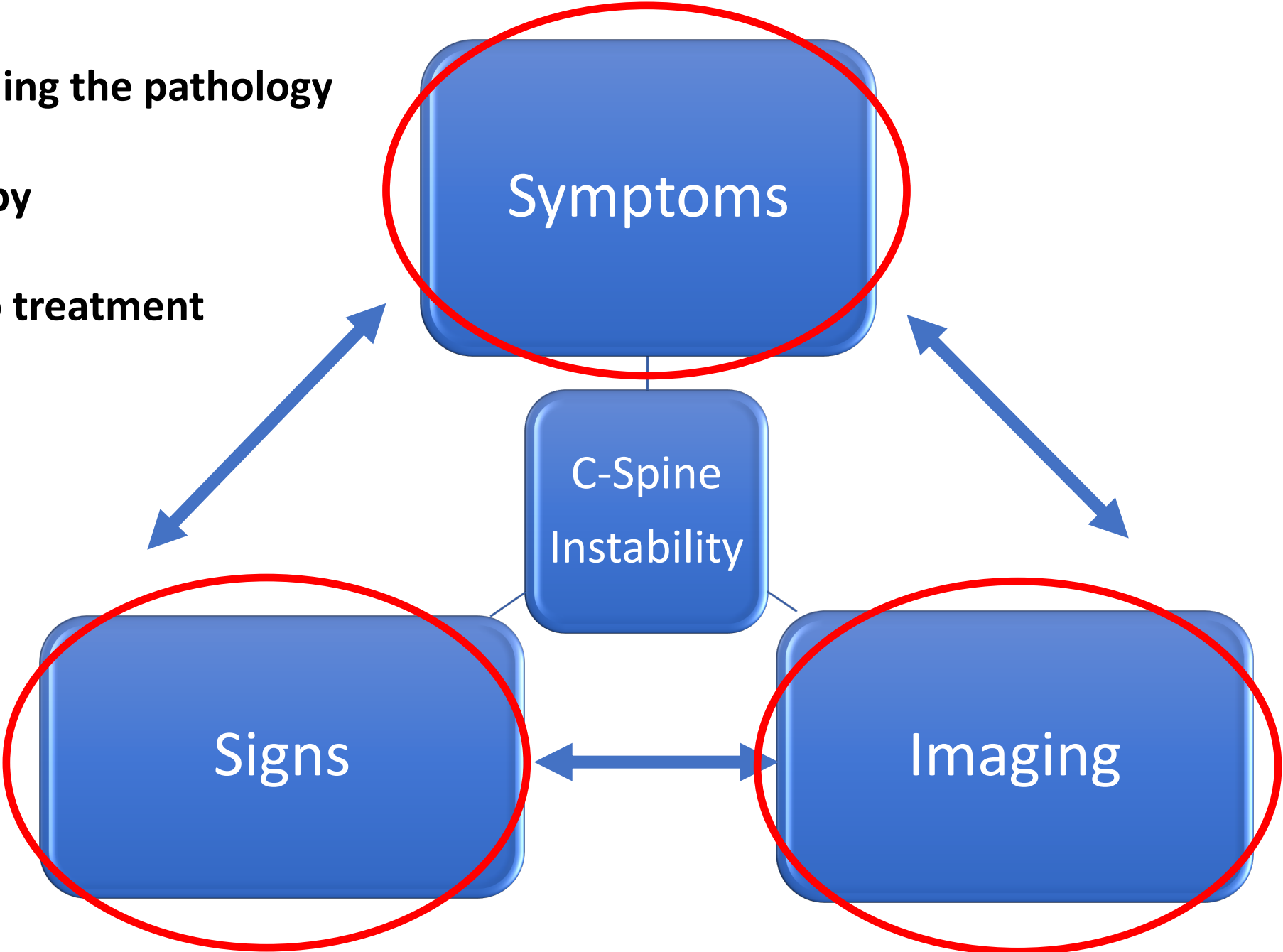
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Understanding the pathology

supported by

response to treatment



Many Organ and System Morbidities in EDS and HSD

Organ Pathologies:

Airway, Cardiovascular,
GI, Bladder

**Neurological:
Concerns:**
CSF pressure
Trapped cord
Nerve compression
Peripheral neuropathy

Neurodiversity:
ASD, ADHD,
DCD, Dyspraxias

**Chronic Fatigue:
Physical &
Cognitive**

**Allergy /
Intolerances /
MCAS**

**Autonomic
Disturbance:**

CVS, GI,
Temp Regulation

**Psychological Health
Concerns:**
Anxiety, Depression

Clinical Assessment of Neck and CCJ

Evidence supports the use of:

- assessment of range of movement
- Neck Disability Index
- Neurological examination

Lemeunier N, da Silva-Oolup S, Chow N, et al. Reliability and validity of clinical tests to assess the anatomical integrity of the cervical spine in adults with neck pain and its associated disorders: Part 1-A systematic review from the Cervical Assessment and Diagnosis Research Evaluation (CADRE) Collaboration. *Eur Spine J.* 2017;26(9):2225-2241

Thoomes EJ, van Geest S, van der Windt DA, et al. Value of physical tests in diagnosing cervical radiculopathy: a systematic review. *Spine J.* 2018;18(1):179-189. doi:10.1016/j.spinee.2017.08.241

Harry Von P, Maloul R, Hoffmann M, Hall T, Ruch MM, Ballenberger N. Diagnostic accuracy and validity of three manual examination tests to identify alar ligament lesions: results of a blinded case-control study. *J Man Manip Ther.* 2019;27(2):83-91. Mansfield CJ, Domnisch C, Iglar L, Boucher L, Onate J, Briggs M. Systematic review of the diagnostic accuracy, reliability, and safety of the sharp-purser test. *J Man Manip Ther.* 2020;28(2):72-81.

Luedtke K, Schoettker-Königer T, Hall T, et al. Concurrent validity and reliability of measuring range of motion during the cervical flexion rotation test with a novel digital goniometer [published correction appears in *BMC Musculoskelet Disord.* 2020 Sep 21;21(1):624]. *BMC Musculoskelet Disord.* 2020;21(1):535. Published 2020 Aug 11. doi:10.1186/s12891-020-03525-6

MacDermid JC, Walton DM, Avery S, et al. Measurement properties of the neck disability index: a systematic review. *J Orthop Sports Phys Ther.* 2009;39(5):400-417.

Clinical Assessment of Neck and CCJ

Evidence supports the use of:

- extension-rotation test,
- Spurling's tests (compression of the cervical spine while it is slightly extended, rotated, and tilted toward one side),
- Squeeze arm sign (for radiculopathy) (squeeze mid 1/3 upper arm)
- shear, rotation, and side-bending stress tests

Lemeunier N, da Silva-Oolup S, Chow N, et al. Reliability and validity of clinical tests to assess the anatomical integrity of the cervical spine in adults with neck pain and its associated disorders: Part 1-A systematic review from the Cervical Assessment and Diagnosis Research Evaluation (CADRE) Collaboration. *Eur Spine J.* 2017;26(9):2225-2241

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Radiological assessment the integrity of CCJ and cervical spine – positional / dynamic imaging

- Symptoms worsen or appear only when a person is upright or performs specific movements.
- Upright and dynamic imaging allows assessment of changes in alignment / angulation on physiological loading and movement, not seen in static and recumbent imaging.
- Significant amount of the literature on ligamentous injury from trauma – whiplash; much less in hypermobility / HM-R disorders

Radiological modalities

Dynamic plain radiographs

Yeo CG, Jeon I, Kim SW. Delayed or Missed Diagnosis of Cervical Instability after Traumatic Injury: Usefulness of Dynamic Flexion and Extension Radiographs. *Korean J Spine*. 2015;12(3):146-149.

Hariharan, K.V., Terhorst, L., Maxwell, M.D. *et al*. Inter-examiner reliability of radiographic measurements from Open-mouth lateral bending cervical radiographs. *Chiropr Man Therap* **28**, 32 (2020). <https://doi.org/10.1186/s12998-020-00317-6>

Digital Motion X-ray (DMX)

Bifulco P, Cesarelli M, Romano M, Fratini A, Sansone M. Measurement of intervertebral cervical motion by means of dynamic x-ray image processing and data interpolation. *Int J Biomed Imaging*. 2013;2013:152920. doi:10.1155/2013/152920

Extension / Flexion supine MRI

Muhle C, Weinert D, Falliner A, et al. Dynamic changes of the spinal canal in patients with cervical spondylosis at flexion and extension using magnetic resonance imaging. *Invest Radiol*. 1998;33(8):444-449. doi:10.1097/00004424-199808000-00004

Upright dynamic MRI

Volle E. Functional magnetic resonance imaging--video diagnosis of soft-tissue trauma to the craniocervical joints and ligaments. *Int Tinnitus J*. 2000;6(2):134-139.

Clivo-axial angle, Grabb Mapstone Oaks, Harris line

Zhang L, Zeitoun D, Rangel A, Lazennec JY, Catonné Y, Pascal-Moussellard H. Preoperative evaluation of the cervical spondylotic myelopathy with flexion-extension magnetic resonance imaging: about a prospective study of fifty patients. *Spine (Phila Pa 1976)*. 2011;36(17):

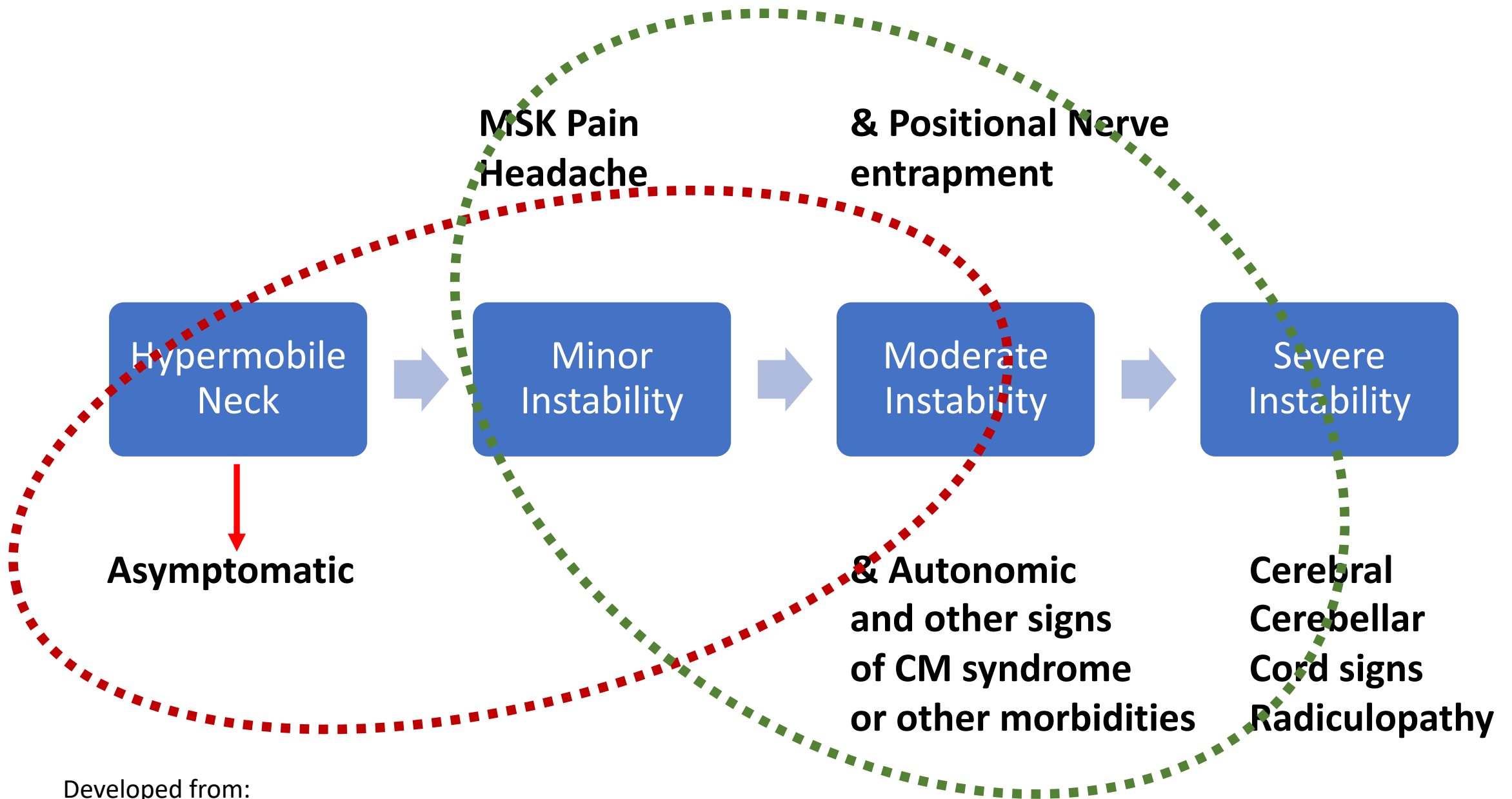
3D Rotation CT CCJ

Bono CM, Vaccaro AR, Fehlings M, et al. Measurement techniques for upper cervical spine injuries: consensus statement of the Spine Trauma Study Group. *Spine*. 2007;32(5):593-600.

Henderson, F.C., Rosenbaum, R., Narayanan, M. *et al*. Atlanto-axial rotary instability (Fielding type 1): characteristic clinical and radiological findings, and treatment outcomes following alignment, fusion, and stabilization. *Neurosurg Rev* **44**, 1553–1568 (2021).

Vascular imaging (CT angio, MRA/V, doppler US)

Jadhav AP, Jovin TG. Vascular imaging of the head and neck. *Semin Neurol*. 2012;32(4):401-410. doi:10.1055/s-0032-1331811



Developed from:
 Steilen D, Hauser R, Woldin B, Sawyer S. Chronic neck pain: making the connection between capsular ligament laxity and cervical instability. *Open Orthop J.* 2014;8:326-345. Published 2014 Oct 1. doi:10.2174/1874325001408010326

Matharu et al. 2020

Headache disorders and craniocervical junction abnormalities in hypermobile Ehlers-Danlos Syndrome. <https://www.ehlers-danlos.com/funded-research/>

McCarthy et al. 2020

Investigating the relationships between functional magnetic resonance imaging, subjective and objective clinical findings in the upper cervical spine in people with hypermobility-related disorders. <https://www.ehlers-danlos.com/funded-research/>

Xu et al. 2020

The value of dynamic MRI in the treatment of cervical spondylotic myelopathy: a protocol for a prospective randomized clinical trial. *BMC Musculoskelet Disord.* 2020;21(1):83. Published 2020 Feb 7. doi:10.1186/s12891-020-3106-y

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General principles of pain management, and management of underlying comorbidities apply :

Physical therapies

Psychological therapies

Drug therapies

Procedures – nerve blocks, facet injections

Multidisciplinary



General physical therapy principles apply:

- In hEDS/HSD people with multiple body area pains reduce symptoms in general by approaches focusing on control around joints
 - Strengthening
 - Posture education
 - Proprioception
 - Mobilization / immobilization
 - Improved motion patterning

Moderate to Severe Instability:

Literature Whiplash associated disorder (WAD) can assist in approaches to physical management

- motor output is impaired in patients with neck pain (Lindstroem et al. 2009)
- muscle composition is altered (De Pauw et al. 2016)
- sensorimotor disturbances can be present (Treleaven et al. 2003)

Moderate to Severe Instability:

- onset of muscle activity is delayed to sudden perturbations (Boudreau et al. 2014)
- Response to strengthening stability of c-spine muscular system
 - RCTs: cervicogenic headache (Jull et al. 2002), chronic idiopathic neck pain (Falla et al. 2013), chronic whiplash (Jull et al. 2007).
 - In WAD, neck specific exercise had 5.3 x higher odds of reducing disability & 3.9 x higher odds of reducing pain (Ludvigsson, et al. *Eur J Pain* 20.2 (2016): 307-315).
- ? Same or adapted approach in HM-R disorders with instability

Other emerging therapies

Prolotherapy – injected material leads to inflammation leads to remodeling of tissue – studies are in the general population / whiplash injury

Centeno CJ, Elliott J, Elkins WL, Freeman M. Fluoroscopically guided cervical prolotherapy for instability with blinded pre and post radiographic reading. *Pain Physician*. 2005;8(1):67-72.

Hooper RA, Frizzell JB, Faris P. Case series on chronic whiplash related neck pain treated with intraarticular zygapophysial joint regeneration injection therapy. *Pain Physician*. 2007;10:313-318.

Hauser, R.A., Steilen D.R., Fisher P. Upper Cervical Instability of Traumatic Origin Treated with Dextrose Prolotherapy: A Case Report. *Journal of Prolotherapy*. 2015;7:e932-e935.

Hauser RA, Lackner JB, Steilen-Matias D, Harris DK. A Systematic Review of Dextrose Prolotherapy for Chronic Musculoskeletal Pain. *Clin Med Insights Arthritis Musculoskelet Disord*. 2016;9:139-159. Published 2016 Jul 7. doi:10.4137/CMAMD.S39160

Stem Cell Therapy - Percutaneous Injection of Cervical Ligaments (PICL) own bone marrow-derived stem cells into the damaged ligaments.

Client endorsements and statements regarding efficacy



Surgery

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Summary

- Headache and neck pain are common findings in EDS / HSD clinics
- The most common symptoms and causes seem similar to those seen in the general population though migraine and cervical spondylosis seem over-represented in clinic
- Assessment requires detailed neurological examination and use of validated clinical tests (examination and assessment of symptoms and disability)
- Treatment for the vast majority of people uses standard principles of pain management and physical therapies.

Summary

- Some individuals present with more complex concerns potentially due to pathology at the craniocervical junction.
- The majority of individuals have no overt Upper or Lower Sensory Motor Neurone signs of cord compression or nerve root entrapment
- The constellation of concerns described in the Cervical Medullary syndrome are challenging to interpret as all of them have other potential causes.
- Correlating clinical signs, symptoms and imaging findings in the absence of neurological signs is challenging given in part the dearth of comparative imaging data for asymptomatic vs symptomatic people with HM or HM-R disorders

Summary

In the absence of neurological signs of compression / tension requiring surgical intervention.

- Conservative treatment is based on principles of pain management in general, and on adapted physical techniques based on principles of managing hypermobility and instability, and on those of neck trauma / whiplash with ensuing ligament laxity.
- Other procedural therapies are emerging (Prolotherapy, Stem Cell Therapy) as potential alternatives to surgical stabilization.



The
**Ehlers
Danlos**
Society™



EDS ECHO SUMMIT SERIES

PRESENTATION

A Physician's Perspective on Cranio-cervical Instability

SPEAKER

Dr Alan Hakim

Consultant Rheumatologist, The Wellington Hospital, London UK

Adjunct Assoc. Prof. in Medicine, PennState, USA

Director of Education, The Ehlers-Danlos Society